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(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : EVANS, Ben, E. [US/US]; 501 Perkiomen Avenue, Lansdale, PA 19446 (US). HOBBS, Douglas, W. [US/US]; 843 Garfield Avenue, Lansdale, PA 19446 (US). PAWLUCZYK, Joseph, M. [US/US]; 1264 Emma Lane, Warminster, PA 18974 (US). PETTIBONE, Douglas, J. [US/US]; 69 Hickory Lane, Shalfont, PA 18914 (US). RITTLE, Kenneth, E. [US/US]; 1955 Old Woods Road, Greenland, PA 18054 (US). WILLIAMS, Peter, D. [US/US]; 260 Shady Nook Road, Harleysville, PA 19446 (US).

(74) Agent: WINOKUR, Melvin; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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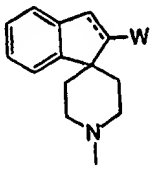
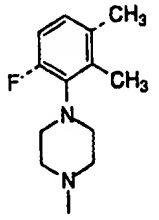
(54) Title: TOCOLYTIC OXYTOCIN RECEPTOR ANTAGONISTS



(I)



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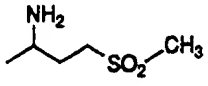
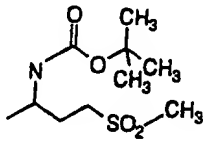


(A)



(B)

(57) Abstract

Compounds of the formula X-Y-Z-R^1, wherein X is (I) or (II); W is hydrogen or acetate; Y is -CO-, -SO_2- -$CO(CH_2)_m$- or -$(CH_2)_m$-; Z is N, O, S, -CHR-, -CR=CH-, -CH=, -$(CH_2)_m$- or -CHCHOH-; R is hydrogen, C_{1-5} alkyl, C_{1-5} alkoxycarbonylamino or quinuclidinylaminocarbonylamino; R^1 is -CH_3, -$CH(CH_3)_2$, C_{1-5} alkoxycarbonyl; aryl, heterocyclic and lowercycloalkyl substituted by R^2 and/or R^3, -NR^4R^5 or -$NCOR^6$; R^2 is hydrogen, hydroxy, carboxyl, acetyl, nitro, halogen, mono-, di- or tri-C_{1-3} alkyl, spirocyclic indenyl, N-spiroindanepiperidinyl, O-R where R is as defined above, O-Het where Het is imidazole or benzimidazole or azimidobenzene, or where R^2 is further defined as -COR^6, -$(CH_2)_m$-$NHCOR^7$, -$(CH_2)_m$$NHCOOR^7$, -$(CH_2)_m$-$NR^8R^9$, -$(CH_2)_m$-NHCO-$(CH_2)_m$$R^7$, -$(CH_2)_m$-NHCO-$CHR^7R^7$, -$(CH_2)_m$-NHCO-CH=$CHR^7$, -$(CH_2)_m$-CO-O-$R^7$, -$(CH_2)_m$-CO-O-$(CH_2)_m$$R^7$, -$(CH_2)_m$-CO-O-$CHR^7R^7$, -$(CH)_m$-CO-O-CH=$CHR^7$, -$NHSO_2$R- where R is as defined above, $NHSO_2R^7$, -$(CH_2)_m$-O-R^{10}, -SO_2R^{10}, -COR^{11}, aryl loweralkyl, alkylsulfonylalkyl, alkylsulfonylalkylamido, R^3 is one or two of hydrogen, hydroxyl or C_{1-5} alkyl; R^4 is hydrogen, C_{1-5} alkyl, or C_{6-10} cycloalkyl; R^5 is hydrogen or acetyl; R^6 is (A) or (B); R^7 is alkylcarbamate alkyl, aryl alkyl or heterocyclyl alkyl substituted by R^{12}, hydrogen, C_{1-4} alkyl, NSO_2R^{12} or NHO-C_{1-4} alkyl; R^8 is hydrogen or C_{1-5} alkyl; R^9 is hydrogen or C_{1-5} alkyl; R^{10} is -CH_3, alkaryl, alkarylalkyl or azimidobenzene; R^{11} is -CH_3, aralkyl or heterocyclylalkyl; R^{12} is hydrogen, C_{1-5} alkyl or C_{1-5} alkoxy; and m is an integer of from 0 to 5. Such compounds are useful as oxytocin and vasopressin antagonists.

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TITLE OF THE INVENTION
TOCOLYTIC OXYTOCIN RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture, such compounds generally pharmacologically useful as agents in obstetric and gynecologic therapy. The aforementioned pharmacologic activities are useful in the treatment of mammals. More specifically, the compounds of the present invention can be used in the treatment of preterm labor, stopping labor preparatory to Caesarean delivery, and in the treatment of dysmenorrhea. At the present time, there is a need in the area of obstetric and gynecologic therapy for such agents.

BACKGROUND OF THE INVENTION

In the field of obstetrics, one of the most important problems is the management of preterm labor. A significant number of the pregnancies progressing past 20 weeks of gestation experience premature labor and delivery, which is a leading cause of neonatal morbidity and mortality. Despite major advances in neonatal care, retention of the fetus in utero is preferred in most instances.

Tocolytic (uterine-relaxing) agents that are currently in use include ß2-adrenergic agonists, magnesium sulfate and ethanol. Ritodrine, the leading ß2-adrenergic agonist, causes a number of cardiovascular and metabolic side effects in the mother, including tachycardia, increased renin secretion, hyperglycemia (and reactive hypoglycemia in the infant). Other ß2-adrenergic agonists, including terbutaline and albuterol have side effects similar to those of ritodrine. Magnesium sulfate at plasma concentrations above the therapeutic range of 4 to 8 mg/dL can cause inhibition of cardiac conduction and neuromuscular transmission, respiratory depression and cardiac arrest, thus making this agent unsuitable when renal function is impaired. Ethanol is as effective as ritodrine in preventing premature

labor, but it does not produce a corresponding reduction in the incidence of fetal respiratory distress that administration of ritodrine does.

It has been proposed that a selective oxytocin antagonist would be the ideal tocolytic agent. In the last few years, evidence has accumulated to strongly suggest that the hormone oxytocin may be a physiological initiator of labor in several mammalian species including humans. Oxytocin is believed to exert this effect in part by directly contracting the uterine myometrium and in part by enhancing the synthesis and release of contractile prostaglandins from the uterine endometrium/decidua. These prostaglandins may, in addition, be important in the cervical ripening process. By these mechanisms, the process of labor (term and preterm) is initiated by a heightened sensitivity of the uterus to oxytocin, resulting in part as a result of a well-documented increase in the number of oxytocin receptors in this tissue. This "up-regulation" of oxytocin receptors and enhanced uterine sensitivity appears to be due to trophic effects of rising plasma levels of estrogen towards term. By blocking oxytocin, one would block both the direct (contractile) and indirect (enhanced prostaglandin synthesis) effects of oxytocin on the uterus. A selective oxytocin blocker, or antagonist, would likely be more efficacious for treating preterm labor than current regimens. In addition, since oxytocin at term has major effects only on the uterus, such an oxytocin antagonizing compound would be expected to have few, if any, side effects.

The compounds of the present invention can also be useful in the treatment of dysmenorrhea. This condition is characterized by cyclic pain associated with menses during ovulatory cycles. The pain is thought to result from uterine contractions and ischemia, probably mediated by the effect of prostaglandins produced in the secretory endometrium. By blocking both the direct and indirect effects of oxytocin on the uterus, a selective oxytocin antagonist can be more efficacious for treating dysmenorrhea then current regimens. An additional use for the present invention is for the stoppage of labor preparatory to Caesarean delivery.

It is, therefore, a purpose of this invention to provide substances which more effectively antagonize the function of oxytocin in disease states in animals, preferably mammals, especially in humans. It is another purpose of this invention to prepare novel compounds which more selectively inhibit oxytocin. It is still another purpose of this invention to provide a method of antagonizing the functions of oxytocin in disease states in mammals. It is also a purpose of this invention to develop a method of preventing or treating oxytocin-related disorders of preterm labor and dysmenorrhea by antagonizing oxytocin.

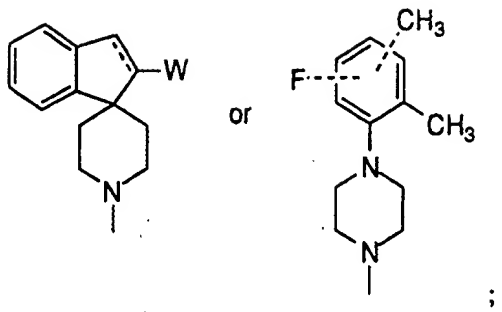
It has now been found that compounds of the present invention are antagonists of oxytocin and bind to the oxytocin receptor. When the oxytocin receptor is bound by the compounds of the present invention, oxytocin is antagonized by being blocked from its receptor and thus being unable to exert its biologic or pharmacologic effects. These compounds are useful in the treatment and prevention of oxytocin-related disorders of animals, preferably mammals and especially humans. These disorders are primarily preterm labor and dysmenorrhea. The compounds would also find usefulness for stoppage of labor preparatory to Caesarean delivery.

SUMMARY OF THE INVENTION

The compounds and their pharmaceutically acceptable salts and esters of the present invention are those of the general structural formula:

$X\text{-}Y\text{-}Z\text{-}R^1$, wherein

X is



;

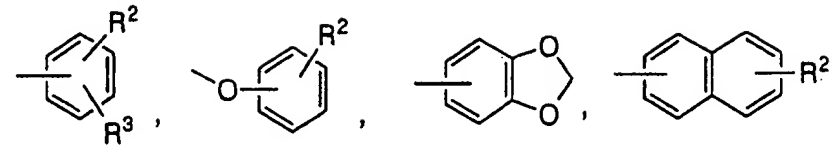
W is hydrogen or acetate;

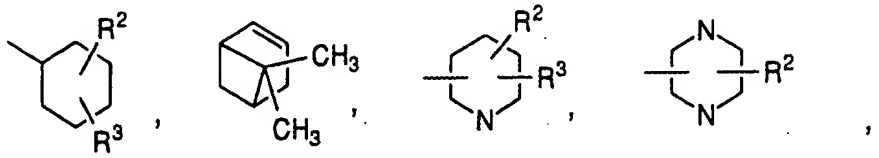
Y is -CO-, -SO_2- -$CO(CH_2)_m$- or -$(CH_2)_m$-;

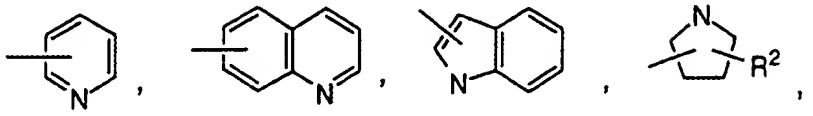
Z is an optional substituent that, when present, is one or more of N, O, S, -CHR-, -CR=CH-, -CH=, -$(CH_2)_m$- or -CHCHOH-;

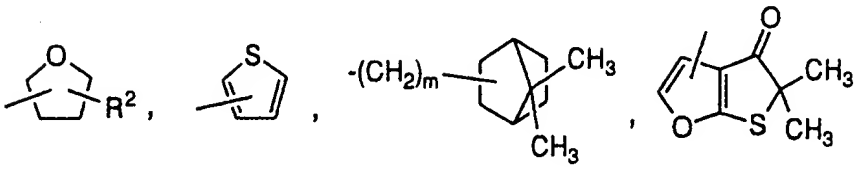
R is hydrogen, C_{1-5} alkyl or C_{1-5} alkoxycarbonylamino, quinuclidinylaminocarbonylamino;

R^1 is -CH_3, -$CH(CH_3)_2$, C_{1-5} alkoxycarbonyl,



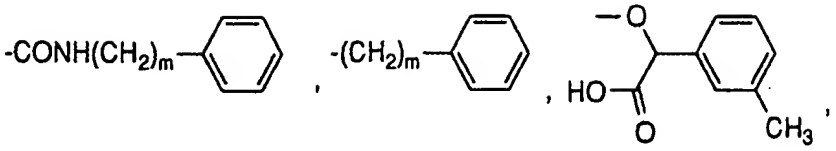


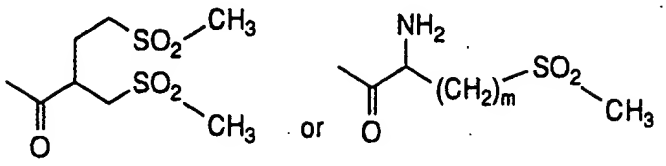




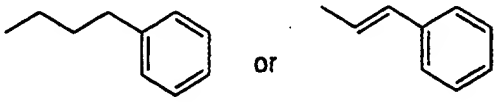
$-NR^4R^5$ or $-NCOR^6$;

R^2 is hydrogen, hydroxy, carboxyl, acetyl, nitro, cis or trand oximino, halogen,
mono-, di- or tri-C_{1-3} alkyl, spirocyclic indenyl,
N-spiroindanepiperidinyl, O-R where R is as defined above, O-Het where Het is imidazole or benzimidazole or azimidobenzene, or where R^2 is further defined as $-COR^6$, $-(CH_2)_m-NHCOR^7$, $-(CH_2)_mNHCOOR^7$, $-(CH_2)_m-NR^8R^9$, $-(CH_2)_m-NHCO-(CH_2)_mR^7$, $-(CH_2)_m-NHCO-CHR^7R^7$, $-(CH_2)_m-NHCO-CH=CHR^7$, $-(CH_2)_m-CO-O-R^7$, $-(CH_2)_m-CO-O-(CH_2)_mR^7$, $-(CH_2)_m-CO-O-CHR^7R^7$, $-(CH)_m-CO-O-CH=CHR^7$, -NHSO2R-where R is as defined above, $NHSO_2R^7$, $-(CH_2)_m-O-R^{10}$, $-SO_2R^{10}$, $-COR^{11}$,





or one to two substituents selected from the group consisting of



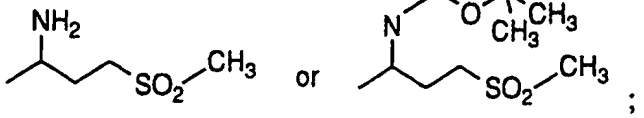
;

R^3 is one or two of hydrogen, hydroxyl or C_{1-5} alkyl;

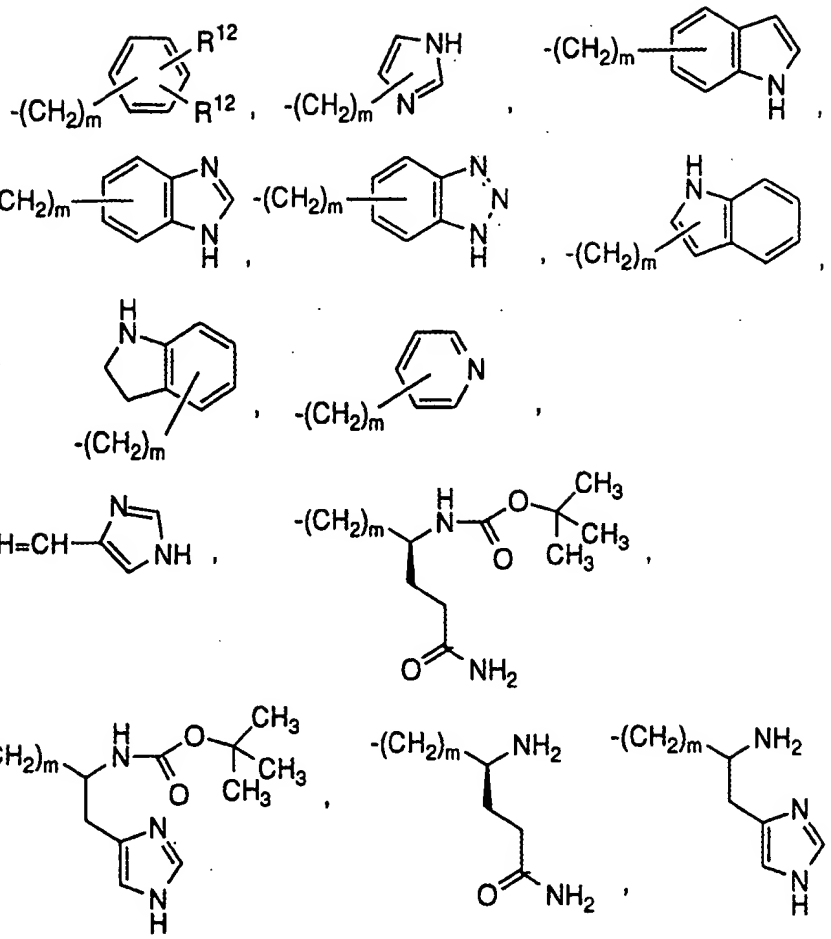
with the proviso that when R^1 is cyclohexyl, then R^2 and R^3 are limited to being hydroxyl or C_{1-5} alkyl;

R^4 is hydrogen, C_{1-5} alkyl, or C_{6-10} cycloalkyl;

R^5 is hydrogen or acetyl;

R^6 is  ;

R^7 is

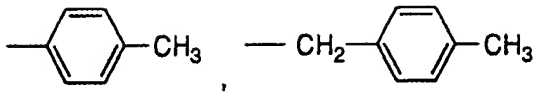


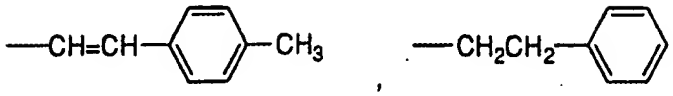
hydrogen, C_{1-4} alkyl, NSO_2R^{12} or NHO-C_{1-4} alkyl;

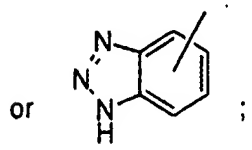
R^8 is hydrogen or C_{1-5} alkyl;

R^9 is hydrogen or C_{1-5} alkyl;

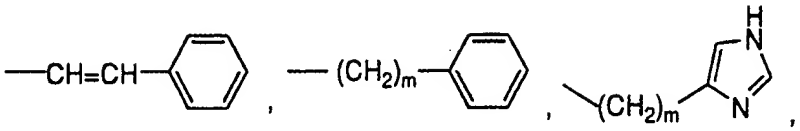
R^{10} is $-CH_3$,

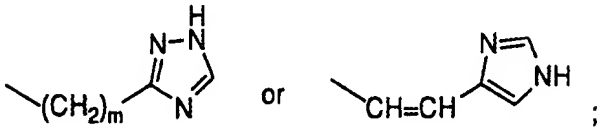






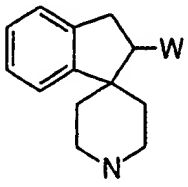
R^{11} is -CH_3,





R^{12} is hydrogen, C_{1-5} alkyl or C_{1-5} alkoxy; and

m is an integer of from 0 to 5;

with the proviso that when X is 

and when R^1 is disubstituted phenyl when the phenyl substituents are any of hydroxyl, carboxyl, nitro, halogen, mono-, di- or tri-C_{1-3} alkyl, C_{1-5} alkoxy; or when R^1 is pyridyl; or when R^1 is $-CH_3$ or $-CH(CH_3)_2$; or when R^1 is unsubstituted bicyclo loweralkyl of 9 carbons or unsubstituted or substituted cyclohexyl and the substituent is hydroxyl; then Y is $-(CH_2)_m-$ where m has a value of from 1 to 5.

Salts and esters encompassed within the term "pharmaceutically acceptable salts and esters" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following salts:

Acetate	Lactobionate
Benzenesulfonate	Laurate
Benzoate	Malate
Bicarbonate	Maleate
Bisulfate	Mandelate
Bitartrate	Mesylate
Borate	Methylbromide
Bromide	Methylnitrate
Calcium Edetate	Methylsulfate
Camsylate	Mucate
Carbonate	Napsylate
Chloride	Nitrate
Clavulanate	N-methylglucamine
Citrate	ammonium salt
Dihydrochloride	Oleate
Edetate	Oxalate
Edisylate	Pamoate (Embonate)
Estolate	Palmitate
Esylate	Pantothenate
Fumarate	Phosphate/diphosphate

Gluceptate	Polygalacturonate
Gluconate	Salicylate
Glutamate	Stearate
Glycollylarsanilate	Sulfate
Hexylresorcinate	Subacetate
Hydrabamine	Succinate
Hydrobromide	Tannate
Hydrochloride	Tartrate
Hydroxynaphthoate	Teoclate
Iodide	Tosylate
Isothionate	Triethiodide
Lactate	Valerate

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this range.

The term "alkenyl" shall mean straight or branched chain alkenes with one or more degrees of unsaturation at any position on the chain, of two to ten total carbon atoms, or any number within this range.

The term "alkynyl" shall mean straight or branched chain alkynes with one or more degrees of unsaturation at any position on the chain, of two to ten total carbon atoms, or any number within this range.

The term ""aryl" shall mean phenyl, naphthyl or fluorenyl.

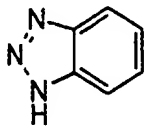
The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms.

Whenever the terms "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g. aralkoxyaryloxy) they shall be interpreted as including those limitations given above for "alkyl" and

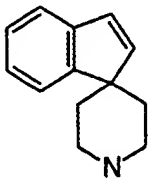
"aryl". Designated numbers of carbon atoms (e.g. C_{1-10}) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The term "oxo" shall refer to the substituent =O.

The term "azimidobenzene" (also known as benzotriazole) shall refer to the moiety



The term "spirocyclic indenyl" shall refer to the moiety



The term "halogen" shall include iodine, bromine, chlorine and fluorine.

The term "preterm labor" shall mean expulsion from the uterus of a viable infant before the normal end of gestation, or more particularly, onset of labor with effacement and dilation of the cervix before the 37th week of gestation. It may or may not be associated with vaginal bleeding or rupture of the membranes.

The term "dysmenorrhea" shall mean painful menstruation.

The term "Caesarean delivery" shall mean incision through the abdominal and uterine walls for delivery of a fetus.

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substitutent.

Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

The ability of the compounds of formula I to antagonize oxytocin makes these compounds useful as pharmacologic agents for mammals, especially for humans, for the treatment and prevention of disorders wherein oxytocin may be involved. Examples of such disorders include preterm labor and especially dysmenorrhea. These compounds may also find usefulness for stoppage of labor preparatory to Cesarean delivery.

Because of the known relationship of vasopressin to oxytocin, the compounds of the present invention are also useful as vasopressin antagonists. Vasopressin antagonists are useful in the treatment or prevention of disease states involving vasopressin disorders, including their use as diuretics and their use in congestive heart failure.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as a tocolytic agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.3-6.0 gm/day orally. Intravenously, the most preferred doses will range from 0.1 to about 10 mg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium

chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, zanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

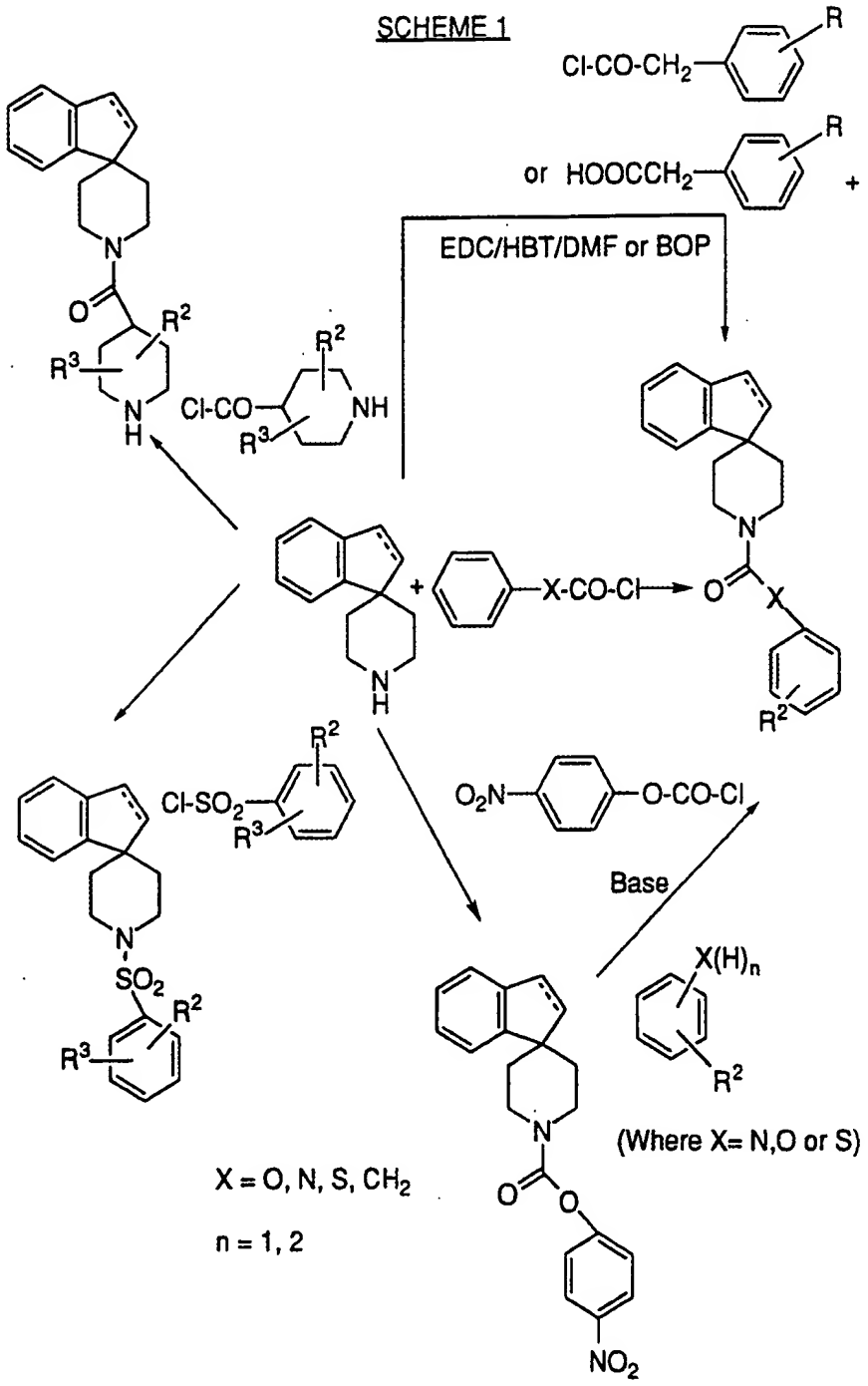
Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropyl- methacrylamide-phenol, polyhydroxyethyl-aspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The compounds of formula I can be prepared readily according to the following reaction Schemes (in which all variables are as defined before) and Examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

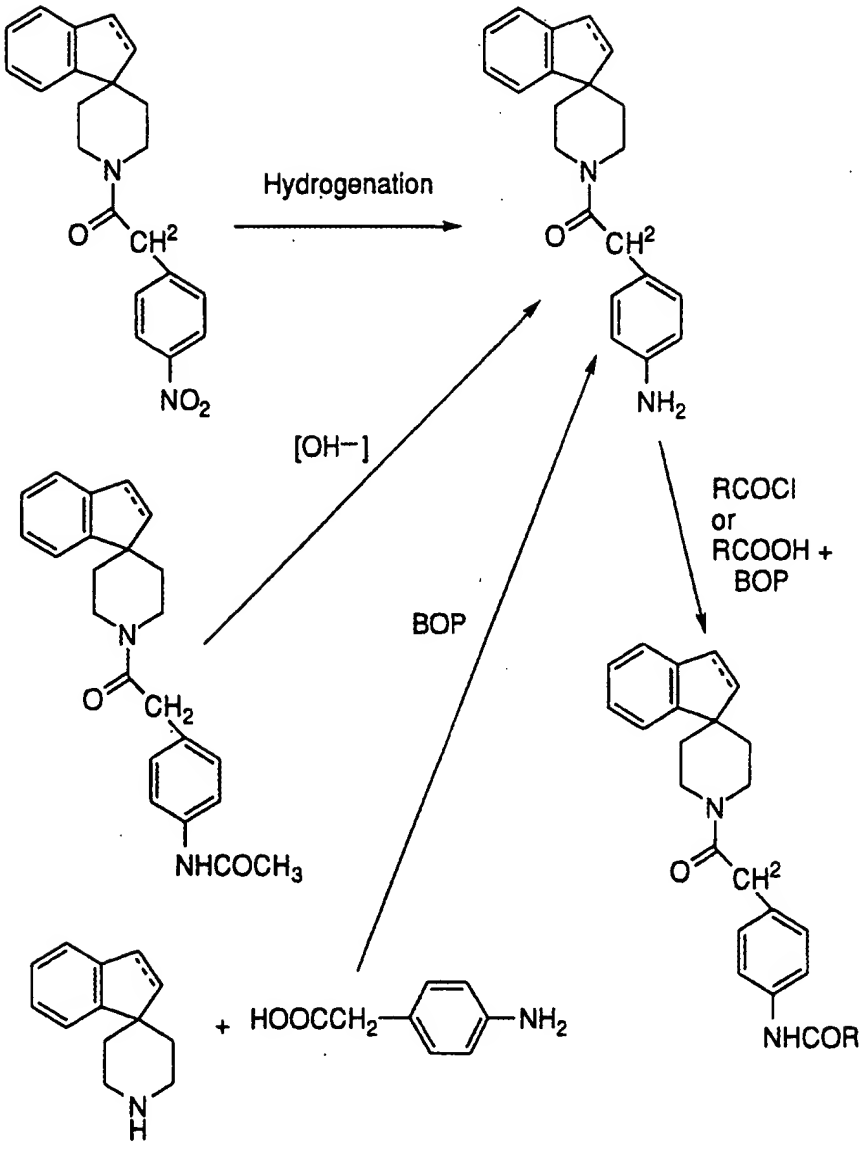
The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for

the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

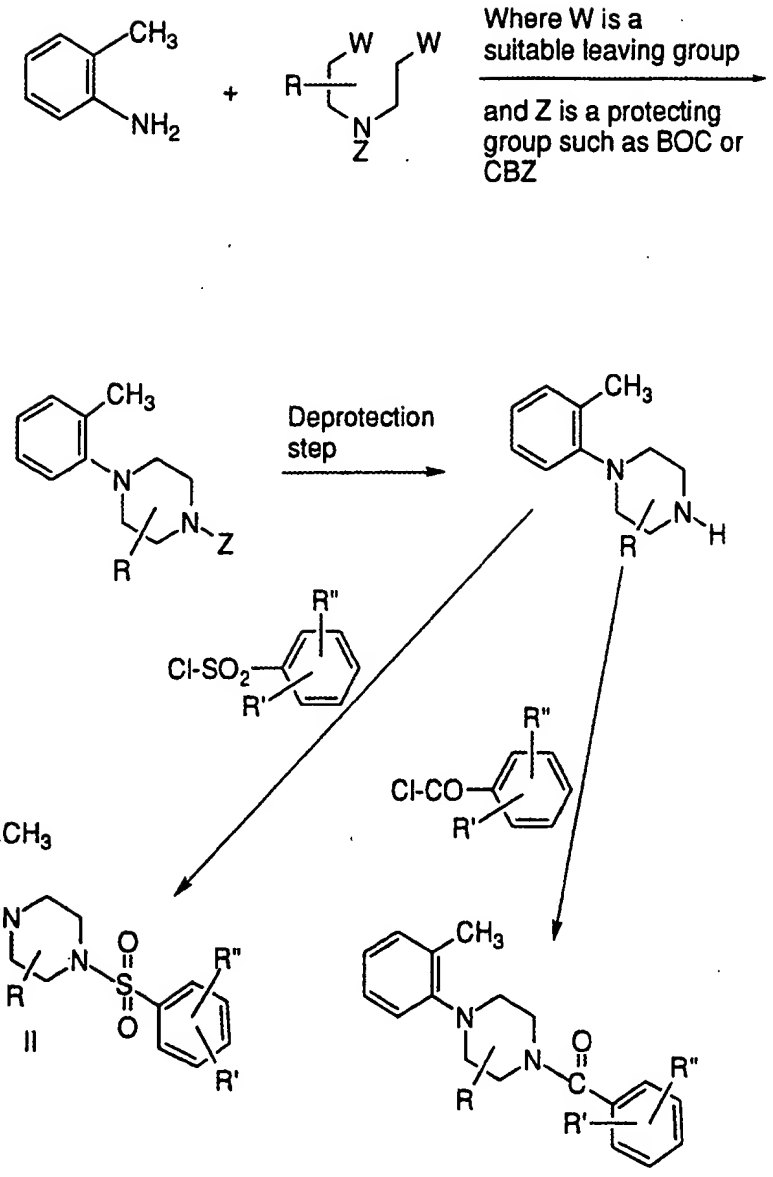
SCHEME 1


Cl-CO-CH2
R
or HOOCCH2
+
EDC/HBT/DMF or BOP
Cl-CO
NH
X-CO-Cl
Cl-SO2
O2N
O-CO-Cl
Base
X(H)n
(Where X= N,O or S)
X = O, N, S, CH2
n = 1, 2

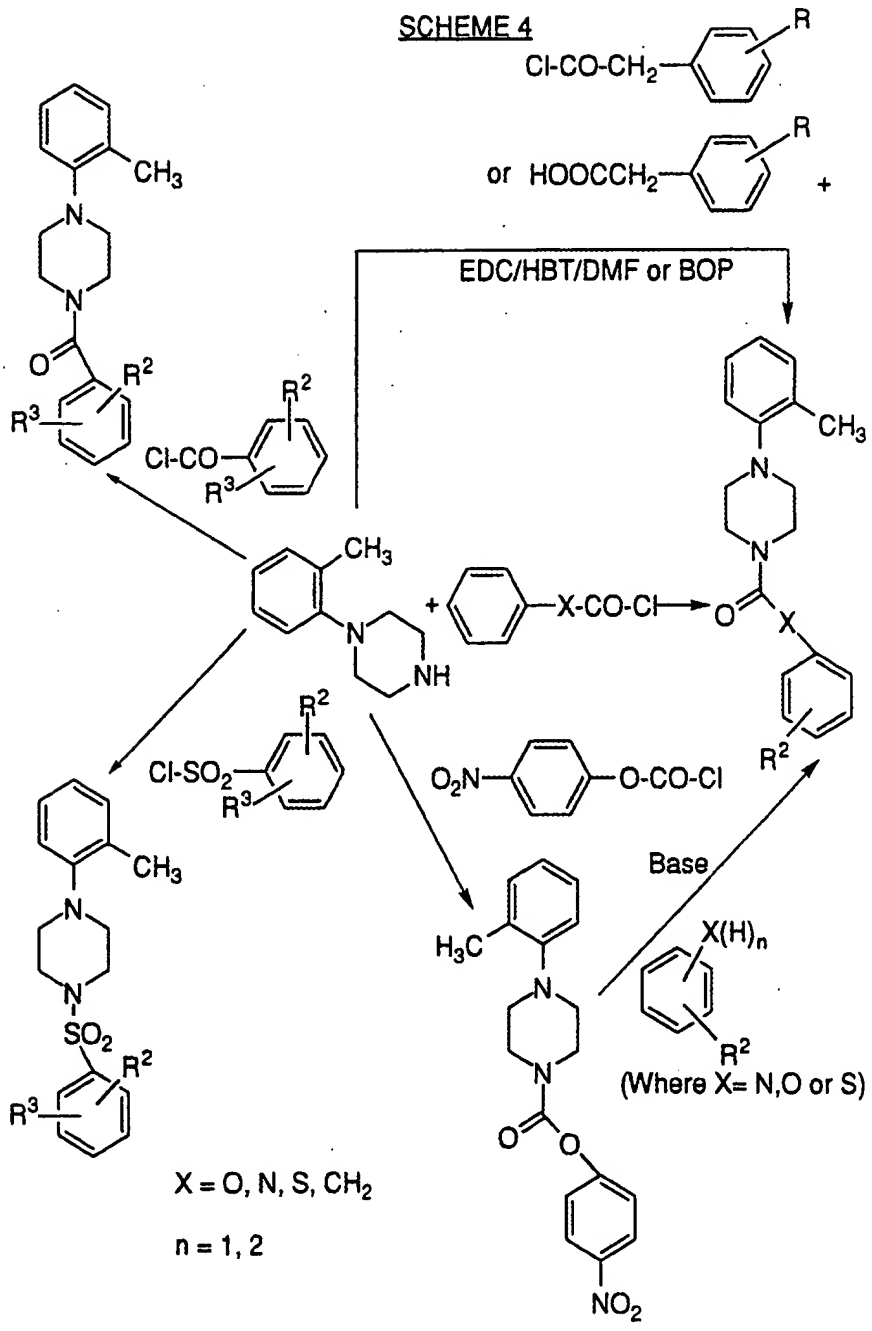
SCHEME 2


Hydrogenation
[OH−]
RCOCl
or
RCOOH +
BOP
BOP
NHCOCH3
NO2
NH2
NHCOR
HOOCCH2
NH2
+

SCHEME 3


CH3
NH2
+
W
W
R
N
Z
Where W is a suitable leaving group
and Z is a protecting group such as BOC or CBZ
Deprotection step
Cl-SO2
R"
R'
Cl-CO
II

SCHEME 4


Cl-CO-CH2
or HOOCCH2
EDC/HBT/DMF or BOP
X-CO-Cl
Cl-SO2
O2N
O-CO-Cl
Base
X(H)n
(Where X= N,O or S)
X = O, N, S, CH2
n = 1, 2

Abbreviations used in the Examples are as follows:

EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

BOC = tert-butoxycarbonyl

TEA = triethylamine

DIEA = diisopropylethylamine

BOP = benzotriazolyloxytris(dimethylamino) phosphonium hexafluorophosphate

THF = tetrahydrofuran

DMF = dimethylformamide

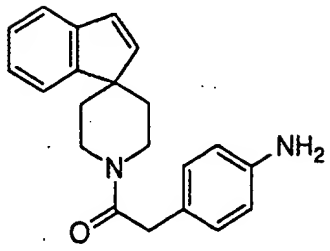
LAH = lithium aluminum hydride

TFA = trifluoroacetic acid

HPLC Method A = 15 min. linear gradient
95:5 A:B to 0:100 A:B
A - H_2O containing 0.1% by vol. TFA
B = CH_3CN containing 0.1% by vol. TFA
2.0 mL/min flow rate
12 cm C_{18} reverse phase column
UV detection (215 nm)

TLC was performed on 20 cm plates coated with silica gel (250 microns) from Analtech.

EXAMPLE 1



70 mg (0.316 mmol) of spiro(1H-indene-1,4'-piperidine HCl) was dissolved in 3 ml DMF and the solution treated with 52.5 mg (0.347 mmol) of 4-aminophenyl acetic acid followed by 161 mg (0.363 mmol) of benzotriazol-1-yl-oxy(dimethylamino)phosphonium hexafluorophosphate (BOP Reagent). The pH of the solution was adjusted to 9.5 with 142 µl (0.794 mmol) of diisopropylethylamine and the mixture stirred at 25° for 1 hour.

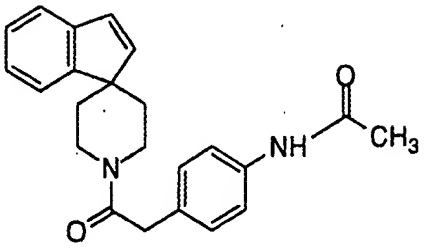
DMF was removed *in vacuo* and the crude residue treated with water and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (1:1 of ethyl acetate: CH_2Cl_2) gave the title compound as a white foam (41 mg, 40.6% yield) upon coevaporation with ether (3x) *in vacuo*.

M.W.:	318.402.
m.p.:	60-87°C (sinter)
HPLC:	96.3%
PMR:	Consistent with structure plus ether and water
M.S.:	M+H = 319 (FAB).
TLC:	R_f = 0.34, Silica GF (1:1 of EtOAc: CH_2Cl_2).
CHN:	Calc'd as $C_{21}H_{22}N_2O \cdot 0.05\ C_4H_{10}O \cdot 0.30\ H_2O$

(F.W. = 327.532):

	C, 77.74;	H, 7.11;	N, 8.55.
Found:	C, 77.83;	H, 6.80;	N, 8.23.

EXAMPLE 2

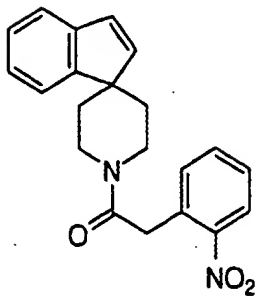


1.1gm (3.45 mmol) of the product of Example 1 was dissolved in 15 ml of CH_2Cl_2 and the solution treated with 0.27 ml (3.80 mmol) of acetyl chloride. The pH was adjusted to 9.5 with 0.55 ml (3.82 mmol) of triethylamine and the mixture stirred at 25°C for 1 hour.

Flash chromatography of the reaction mixture directly on silica gel (3:1 of ethyl acetate: CH_2Cl_2) gave the title compound as a crystalline solid (992 mg, 79.3% yield) from ethyl acetate.

M.W.	360.438.		
m.p.:	217-9°C.		
HPLC:	99.5%		
PMR:	Consistent with structure.		
M.S.:	M+H = 361 (FAB).		
TLC:	R_f = 0.31, Silica GF (3:1 of ethyl acetate: CH_2Cl_2).		
CHN:	Calc'd as $C_{23}H_{24}N_2O_2$:		
	C, 76.64;	H, 6.71;	N, 7.77.
Found:	C, 76.26;	H, 6.80;	N, 7.76.

EXAMPLE 3



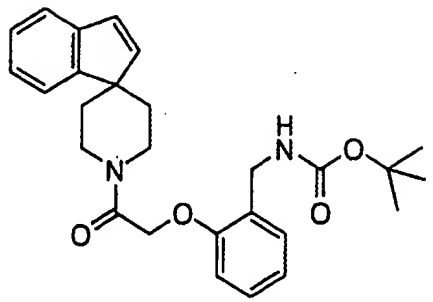
125 mg (0.564 mmol) of spiro(1H-indene-1,4'-piperidine) hydrochloride was dissolved in 3 ml DMF and the solution treated with 112 mg (0.620 mmol) of o-nitrophenyl acetic acid followed by 286 mg (0.649 mmol) of benzotriazol-1-yl-oxytris-(dimethylamino)-phosphonium hexafluorophosphate (BOP reagent). The pH of the solution was adjusted to 9.5 with 307 µl (1.75 mmol) of diisopropyl ethylamine and the mixture stirred at 25°C for 1 hour.

DMF was removed *in vacuo* and the crude residue treated with H_2O and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (3% Et_2O in CH_2Cl_2) gave 155.7 mg (79.4% yield) of the title compound as a white foam after evaporation *in vacuo*.

M.W.:	348.386.
m.p.:	60-75°C (sinter).
HPLC:	93.4%.
PMR:	Consistent with structure plus water.
M.S.:	M+H = 349.2 (FAB).
TLC:	Rf = 0.29, Silica GF (4% Et_2O in CH_2Cl_2).
CHN:	Calc'd as $C_{21}H_{20}N_2O_3 \cdot 0.30\ H_2O$ (F.W. = 353.8): C, 71.28; H, 5.87; N, 7.92.

Found: C, 71.35; H, 5.64; N, 7.91.

EXAMPLE 4



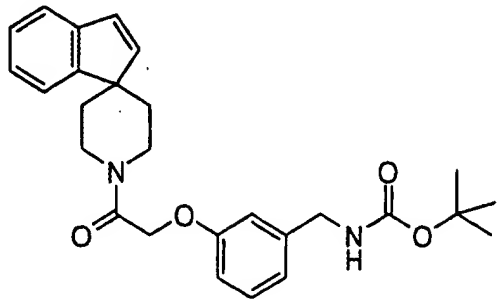
250 mg (1.13 mmol) spiro(1H-indene-1,4'-piperidine) hydrochloride was dissolved in 10 ml DMF and the solution treated with 350 mg (1.24 mmol) of 2-(t-butyloxyaminomethyl)-phenylacetic acid followed by 575 mg (1.30 mmol) of benzotriazol-1-yloxytris (dimethylamino)phosphonium hexafluorophosphate (BOP Reagent). The pH of the solution was adjusted to 9.5 with diisopropylethylamine and the mixture stirred at 25°C for 1 hour.

DMF was removed *in vacuo* and the crude residue treated with water and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (13% Et_2O in CH_2Cl_2) gave the title compound isolated as a crystalline solid (285 mg, 56% yield) from diethyl ether.

M.V.: 448.542.
m.p.: 165-7°C.
HPLC: 97.2%.
PMR: Consistent with structure plus ether.
M.S.: M+H + Thioglycerol (M.W. = 108) = 5573 (FAB).
TLC: R_f = 0.48, Silica GF (20% ET_2O in CH_2Cl_2).

CHN: Calc'd as $C_{27}H_{32}N_2O_4 \cdot 0.10\ C_4H_{10}O$ (F.W. = 455.954)
C, 72.17; H, 7.30; N, 6.14.
Found: C, 72.12; H, 7.33; N, 6.29.

EXAMPLE 5



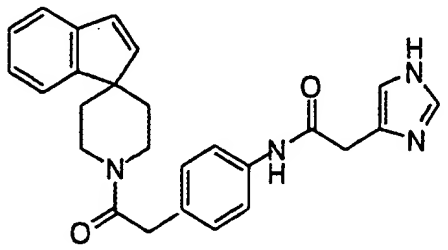
250 mg (1.13 mmol) of spiro(1H-indene-1,4'-piperidene) hydrochloride was dissolved in 10 ml DMF and the solution treated with 350 mg (1.24 mmol) of 3-(t-butyloxyaminomethyl)-phenyl acetic acid followed by 575 mg (1.30 mmol) of benzotriazol-1-yloxytris(dimethyl-amino)phosphonium hexafluorophosphate (BOP Reagent). The pH of the solution was adjusted to 9.5 with 550 µl (3.14 mmol) of diisopropyl-ethylamine and the mixture stirred at 25°C for 1 hour.

DMF was removed *in vacuo* and the crude residue treated with water and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), dried over Na_2SO_4, filtered, and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (20% Et_2O in CH_2Cl_2) gave the title compound as a white foam (328 mg, 65.0% yield) upon coevaporation with ether (3x) *in vacuo*.

M.W.: 448.542.
m.p.: 55-72°C (sinter).
HPLC: 99.6%
PMR: Consistent with structure plus water.

M.S.: M+H + Thioglycerol (M.W. = 108) = 557.6 (FAB).
TLC: Rf = 0.52, Silica GF (25% Et_2O in Ch_2Cl_2).
CHN: Calc'd as $C_{27}H_{32}N_2O_4 \cdot 0.15\ H_2O$ (F.W. = 451.269):
C, 71.86; H, 7.21; N, 6.21.
Found: C, 71.83; H, 7.09; N, 6.45.

EXAMPLE 6



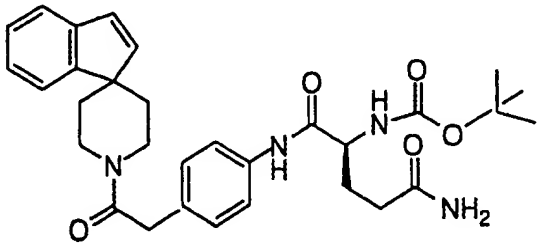
70 mg (0.220 mmol) of the product of Example 1 was dissolved in 5 ml DMF and the solution treated with 39.3 mg (0.242 mmol) of imidazole-4-acetic acid-hydrocloride followed by 32.7 mg (0.242 mmol) of 1-hydroxybenzotriazole hydrate (HBT) and 46.4 mg (0.242 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimidehydrochloride (EDC). The pH was adjusted to 9.5 with triethylamine and the mixture stirred at 25°C or 4 hours.

DMF was removed *in vacuo* and the crude residue treated with water and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (100:10:1 of CH_2Cl_2:MeOH: Conc NH_4OH) gave the title compound as a white solid (50.8 mg, 54.2% yield) after evaporation *in vacuo* and trituration with ether.

M.W.: 426.50.
m.p.: 104-36°C (sinter).

HPLC:	99.3%
PMR:	Consistent with structure plus ether, CH_2Cl_2, and water.
M.S.:	M+H + 427.1 (FAB).
TLC:	R_f = 0.32, Silica GF (80:10:1 of CH_2Cl_2: MeOH: Conc. NH_4OH).
CHN:	Calc'd a $C_{26}H_{26}N_4)2 \cdot 0.10\ CH_2Cl_2 \cdot 0.10$: $C_4H_{10}O \cdot 0.50\ H_2O$ (F.W. = 451.212):
	C, 70.53; H, 6.26; N, 12.42.
Found:	C, 70.56; H, 6.04; N, 12.64.

EXAMPLE 7



85 mg (0.267 mmol) of the product of Example 1 was dissolved in 5 ml DMF and the solution treated with 72.3 mg (0.294 mmol) of N-t-butyloxycarbonyl-L-glutamine followed by 39.7 mg (0.294 mmol) of 1-hydroxybenzotriazole hydrate (HBT) and 56.3 mg (0.294 mmol of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC). The pH was adjusted to 9.5 with 55 µl (0.395 mmol) of triethylamine (Et3N) and the mixture stirred at 25°C for 1.5 hours.

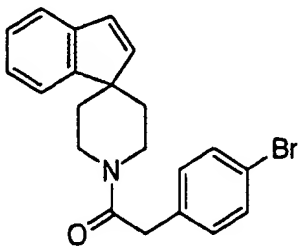
A second portion of 72.3 mg (0.294 mmol) of N-t-butyloxy-carbonyl-L-glutamine, 39.7 mg (0.294 mmol) of HBT, 56.3 mg (0.294 mmol) of EDC and 55 µl (0.395 mmol) of Et3N was added and the mixture stirred at 25°C for 18 hours.

DMF was removed *in vacuo* and the residue treated with H_2O and extracted with ethyl acetate (3x). The organic extracts were com-

bined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (6% MeOH in CH_2Cl_2) gave the title compound as a white solid (57.4 mg, 39.3% yield) after evaporation *in vacuo* and trituration with ether.

M.W.:	546.646.			
m.p.:	104-47°C (sinter).			
HPLC:	99.1%.			
PMR:	Consistent with structure plus water and ether.			
M.S.:	M+H = 547 (FAB).			
TLC:	R_f = 0.18, Silica GF (4% MeOH in CH_2Cl_2).			
CHN:	Calc'd as $C_{31}H_{38}N_4O_5 \cdot 0.10\ C_4H_{10}O \cdot 0.75\ H_2O$ (F.W. = 5657.597):			
	C, 66.44;	H, 7.19;	N, 9.87.	
Found:	C, 66.42;	H, 6.98;	N, 10.04.	

EXAMPLE 8



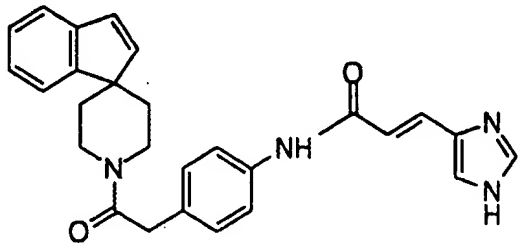
75 mg (0.338 mmol) of spiro(1H-indene-1,4'-piperidine) hydrochloride was dissolved in 3 ml DMF and the solution treated with 80.0 mg (0.372 mmol) of 4-bromophenyl acetic acid followed by 171.9 mg (0.389 mmol) of benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP Reagent). The pH of the solution was adjusted

to 9.5 with 125 ml (0.710 mmol) of diisopropylethylamine and the mixture stirred at 25°C for 1 hour.

DMF was removed *in vacuo* and the crude residue treated with water and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (5% Et_2O in CH_2Cl_2) gave the title compound as a white foam (30 mg, 23.3% yield) upon coevaporation with ether (3x) *in vacuo*.

M.W.:	= 382.282.
m.p.:	44-58°C (sinter).
HPLC:	99.5%.
PMR:	Consistent with structure plus water.
M.S.:	M+H = 382.1/384.1 at 1/1 (FAB).
TLC:	R_f = 0.44, Silica GF (6% Et_2O in Ch_2Cl_2).
CHN:	Calc'd as $C_{21}H_{20}BrNO \cdot 0.40\ H_2O$ (F.W. = 389.513):
	C, 64.75; H, 5.38; N, 3.60.
Found:	C, 64.51; H, 5.06; N, 3.60.

EXAMPLE 9



375 mg (1.18 mmol) of the product of Example 1 was dissolved in 10 ml DMF and the solution treated with 179 mg (1.30 mmol) of urocanic acid followed by 175 ml (1.29 mmol of 1-hydroxybenzo-

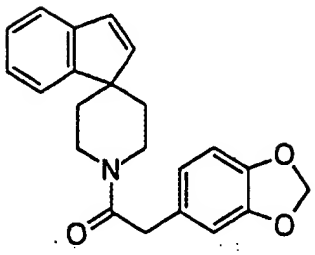
triazole hydrate (HBT) and 248.5 mg (1.30 mmol) of 1-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide hydrochloride (EDC). The pH of the solution was adjusted to 9.5 with 414 µl (0.298 mmol) of triethylamine (Et_3N) and the reaction stirred at 25°C for 6 hours.

A second portion consisting of 179 mg (1.30 mmol) of urocanic acid, 175 mg (1.29 mmol) of HBT, 249 (1.30 mmol) of EDC and 414 µl (0.298 mmol) of Et_3N was added and the reaction stirred at 25°C for 18 hours.

DMF was removed *in vacuo* and the residue treated with water and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (100:10:1 of CH_2Cl_2: MeOH: Conc. NH_4OH) gave the title compound as a crystalline solid (106 mg, 20.5% yield) from ethyl acetate.

M.W.: = 438.51.
m.p.: 170-85°C (Physical Change); 228-30°C (melt).
HPLC: 99.0%.
PMR: Consistent with structure plus water.
M.S.: M+H = 439 (FAB).
TLC: R_f = 0.36, silica GF (80:10:1 of CH_2Cl_2: MeOH: Conc. NH_4OH).
CHN: Calc'd as $C_{27}H_{26}N_4O_2 \cdot 0.95\ H_2O$ (F.W.455.468):
C, 71.17; H, 6.17; N, 12.30.
Found: C, 71.05; H, 5.78; N, 11.91.

EXAMPLE 10

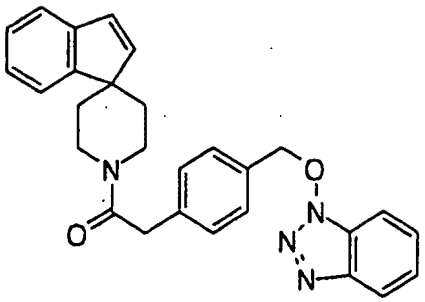


60 mg (0.271 mmol) of spiro(1H-indene-1,4'-piperidine) hydrochloride was dissolved in 4 ml DMF and the solution treated with 53.7 mg (0.298 mmol) of 3,4-methylenedioxy phenyl acetic acid followed by 137.8 mg (0.312 mmol) of benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate (BOP Reagent). The pH of the solution was adjusted to 9.5 with 100 µl (0.569 mmol) of diisopropylethylamine and the mixture stirred at 25°C for 1 hour.

DMF was removed *in vacuo* and the crude residue treated with water and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (6% Et_2O in CH_2Cl_2) gave the title compound as a crystalline solid (32.4 mg, 34.3% yield) from ether.

M.W.:	347.396.		
m.p.:	123-5°C.		
HPLC:	99.4%		
PMR:	Consistent with structure plus water.		
M.S.:	M+H = 348.1 (FAB).		
TLC:	Rf = 0.30, Silica GF (6% Et_2O in Ch_2Cl_2)		
CHN:	Calc'd as $C_{22}H_{21}NO_3 \cdot 0.15\ H_2O$ (F.W. = 350.119):		
	C, 75.47;	H, 6.13;	N, 4.00.
Found:	C, 75.51;	H, 5.79;	N, 4.01.

EXAMPLE 11



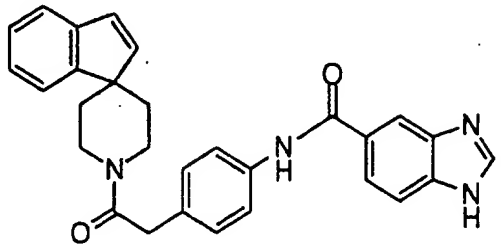
300 mg (1.35 mmol) of spiro(1H-indene-1,4'-piperidine) hydrochloride was dissolved in 10 ml DMF and the solution treated with 341 mg (1.49 mmol) of p-bromoethyl phenyl acetic acid followed by 687 mg (1.55 mmol) of benzotriazol-1-yloxy(dimethylamino) phosphonium hexafluorophosphate (BOP Reagent). The pH of the solution was adjusted to 9.5 with 769 µl (4.39 mml) of diisopropylethylamine and the mixture stirred at 25°C for 18 hours.

DMF was removed *in vacuo* and the crude residue treated with water and extracted with ethyl acetate (3x). The oganic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (12% Et_2O in CH_2Cl_2) gave the title compound as a white foam (318 mg, 59.3% yield) upon coevaporation with ether (3x) *in vacuo*.

M.W.:	450.52.
m.p.:	50-64°C.
HPLC:	94.9%.
PMR:	Consistent with structure plus water.
M.S.:	M+H = 451 (FAB).
TLC:	R_f = 0.27, silica GF (15% Et_2O in CH_2Cl_2).

CHN: Calc'd as $C_{28}H_{26}N_4O_2 \cdot 1.30\ H_2O$ (F.W. = 473.965):
C, 70.95; H, 6.08; N, 11.82.
Found: C,70.98; H, 5.81; N, 12.00.

EXAMPLE 12



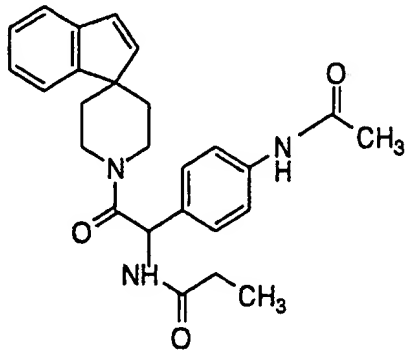
60 mg (0.188 mmol) of the product of Example 1 was dissolved in 3 ml DMF and the solution treated with 36.6 mg (0.226 mmol) of benzoimidazole-5-carboxylic acid followed by 30.5 mg (0.226 mmol) of 1-hydroxybenzotriazole hydrate (HBT) and 43.3 mg (0.226 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC). The pH was adjusted to 9.5 with 63.0 µl (0.453 mmol) of triethylamine and the mixture stirred at 25°C for 20 hours.

A second portion consisting of 18.3 mg (0.226 mmol) of benzoimidazole-5-carboxylic acid, 15.3 mg (0.113 mmol) HBT, 21.7 mg (0.113 mmol) EDC and 31.5 µl (0.227 mmol) of triethylamine was added and the reaction stirred at 25°C for 6 hours.

DMF was removed *in vacuo* and the residue treated with water and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (100:10:1 of CH_2Cl_2:MeOH:Conc. NH_4OH) gave the title compound as a crystalline solid (51.5 mg, 59.1% yield) from ethyl acetate.

M.W.:	462.53.	
m.p.:	212-6°C.	
HPLC:	98.8%.	
PMR:	Consistent with structure.	
M.S.:	M+H=463 (FAB).	
TLC:	Rf = 0.34, silica GF (80:10:1 of Cl_2:MeOH:Conc NH_4OH).	
CHN:	Calc'd as $C_{29}H_{26}N_4O_2$: (m.w. - 462.53):	
	C, 75.30;	H, 5.67; N, 12.11.
Found:	C, 75.18;	H, 5.66; N, 12.06.

EXAMPLE 13



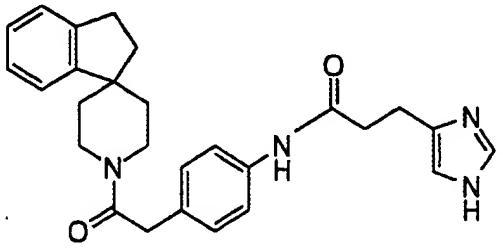
100 mg (0.451 mmol) of spiro(1H-indene-1,4'-piperidine) hydrochloride was dissolved in 3 ml DMF N-ethoxycarbonyl-α-(4-Acetamidophenyl)-glycine followed by 229 mg (0.519 mmol) of benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluoro-phosphate (BOP Reagent). The pH of the solution was adjusted to 9.5 with 166 µl (0.947 mmol) of diisopropylethylamine and the mixture stirred at 25°C for 1 hours.

DMF was removed *in vacuo* and the crude residue treated with water and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude

product on silica gel (3% MeOH in CH_2Cl_2) gave the title compound isolated as a crystalline solid (139 mg, 68.8% yield) from ether.

M.W.:	447.516.	
m.p.:	216-8°C.	
HPLC:	98.1%.	
PMR:	Consistent with structure.	
M.S.:	M+H=448.1 (FAB).	
TLC:	R_f = 0.27, silica GF (4% MeOH in CH_2Cl_2).	
CHN:	Calc'd as $C_{26}H_{29}N_3O_4$ (F.W. - 447.516):	
	C, 69.78;	H, 6.53; N, 9.39.
Found:	C, 69.67;	H, 6.51; N, 9.55.

EXAMPLE 14

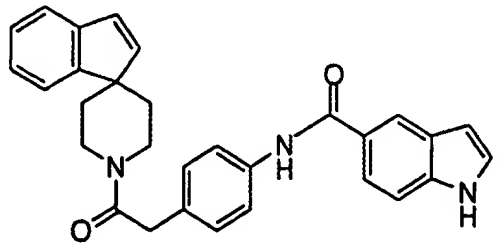


74.4 mg (0.170 mmol) of the product of Example 9 was dissolved in 10 ml of absolute ethanol, treated with 15 mg 10% Pd on C under a nitrogen atmosphere, and hydrogenated at 60 psi for 3 hours. The mixture was filtered through Solka Floc® to remove catalyst and the filter pad was washed thoroughly with fresh absolute ethanol. The filtrate was evaporated to dryness *in vacuo* and the residue was flash chromatographed on silica gel (60:10:1 of CH_2Cl_2:MeOH:H_2O:HoAc). The product fractions were combined, stripped to dryness *in vacuo*, and the residue treated with dilute NaHCO3(aq) and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), dried over

Na_2SO_4, filtered and stripped to dryness *in vacuo*. The residue was coevaporated with ether (3x), then triturated with ether and filtered to give the title compound as a white solid (44.8 mg, 59.7% yield).

M.W.:	442.542.			
m.p.:	89-128°C.			
HPLC:	99.6%.			
PMR:	Consistent with structure plus ether, ethyl acetate and water.			
M.S.:	M+H=443.1 (FAB).			
TLC:	Rf = 0.29, silica GF (60:10:1:1 of CH_2Cl_2:MeOH:H_2O:HoAc).			
CHN:	Calc'd as $C_{27}H_{30}N_4O_2 \cdot 0.15\ C_4H_{10}O \cdot 0.10\ C_4H_8O_2 \cdot 0.35$			
H_2O:				
	C, 71.74;	H, 7.10;	N, 11.95.	
Found:	C, 71.68;	H,7.05;	N, 11.75.	

EXAMPLE 15

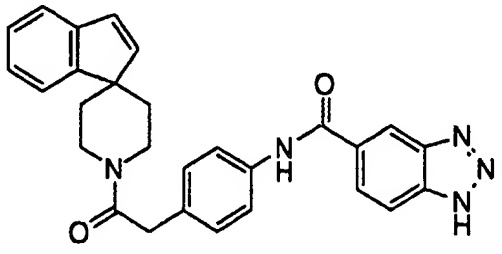


50 mg (0.157 mmol) of the product of Example 1 was dissolved in 2 ml DMF and the solution treated with 27.8 mg (0.173 mmol) of indole-5-carboxylic acid followed by 23.3 mg (0.173 mmol of 1-hydroxybenzotriazole hydrate (HBT) and 33.1 mg (0.173 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC). The pH of the solution was adjusted to 9.5 with 49 µl (0.350 mmol) of triethylamine and the reaction stirred at 25°C for 1 hour.

A second portion consisting of 13.0 mg (0.081 mmol) of indole-5-carboxylic acid, 12.0 mg (0.089 mmol) HBT, 15.0 mg (0.078 mmol) EDC, and 22.1 µl (0.159 mmol) of triethylamine was added and the reaction stirred at 25°C for 1 hour. DMF was removed *in vacuo* and the residue treated with water and extracted with ethyl acetate (3x). The organic layers were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped to dryness *in vacuo*. Flash chromatography of the crude product on silica gel (230:10:1 of CH_2Cl_2:MeOH:Conc. NH_4OH) gave the title compound as an off-white solid (30.0 mg, 37.6% yield) upon trituration with ethyl acetate.

M.W.:	461.54.
m.p.:	241-3°C.
HPLC:	97.7%.
PMR:	Consistent with structure plus water.
M.S.:	M+H=462 (FAB).
TLC:	R_f = 0.25, silica GF (200:10:1 of CH_2Cl_2:MeOH:conc. NH_4OH)
CHN:	Calc'd as $C_{30}H_{27}N_3O_2 \cdot 0.75\ H_2O$. (F.W.=492.701):
	C, 75.08; H, 6.16; N, 8.53.
Found:	C, 74.97; H,. 5.80; N, 8.47.

EXAMPLE 16

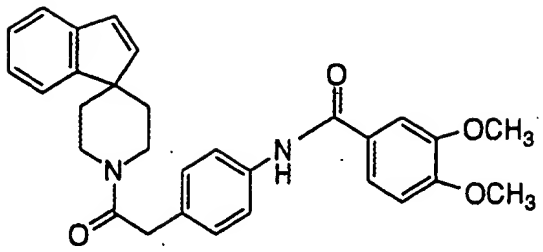


55 mg (0.173 mmol) of the product of Example 1 was dissolved in 2 ml DMF and the solution was treated with 33.9 mg (0.208 mmol) of benzotriazole-5-carboxylic acid followed by 28.1 mg (0.208 mmol) of 1-hydroxybenzotriazole hydrate (HBT) and 39.9 mg (0.208 mmol of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC). The pH of the solution was adjusted to 9.5 with 66.6 µl (0.478 mmol) of triethylamine and the reaction stirred at 25°C for 18 hours.

DMF was removed *in vacuo* and the residue treated with water and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and stripped in dryness *in vacuo*. Flash chromatography of the crude product on silica gel (88:10:1 of CH_2Cl_2:MeOH: Conc. NH_4OH) gave the title compound as a crystalline solid (39.8 mg, 49.8% yield from ethyl acetate.

M.W.:	463.52.		
m.p.:	229-32°C.		
HPLC:	99.6%		
PMR:	Consistent with structure plus ethyl acetate.		
M.S.:	M+H=464 (FAB).		
TLC:	R_f = 0.33, silica GF (80:10:1 of CH_2Cl_2:MeOH:Conc. NH_4OH)		
CHN:	Calc'd as $C_{28}H_{25}N_5O_2 \cdot 0.05\ C_4H_8O_2$ (F.W. = 467.948):		
	C, 72.38;	H, 5.47;	N, 14.97.
Found:	C, 72.39;	H, 5.33;	N, 14.92.

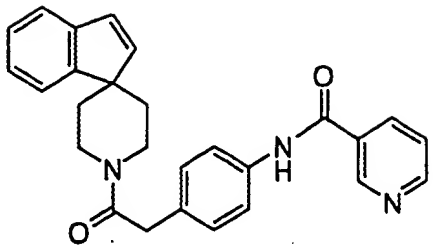
EXAMPLE 17



55.0 mg (0.173 mmol) of the product of Example 1 was dissolved in 3 ml CH_2Cl_2 and the solution treated with 37.9 mg (0.189 mmol) of 3,4-dimethoxybenzoyl chloride. The pH of the solution was adjusted to 9.5 with 28.0 µl (0.201 mmol) of triethylamine and the mixture stirred at 25°C for 15 minutes. Flash chromatography of the reaction mixture directly on silica gel (40% Et_2O in CH_2Cl_2) gave the title compound as a white solid (20.0 mg, 24.0% yield) upon trituration with ether.

M.W.:	482.556.		
m.p.:	107-18°C (shrink).		
HPLC:	99.6%.		
PMR:	Consistent with structure plus ether and water.		
M.S.:	= M+H = 483 (FAB).		
TLC:	R_f = 0.26, silica GF (40% Et_2O in CH_2Cl_2).		
CHN:	Calc'd as $C_{30}H_{30}N_2O_4 \cdot 0.15\ C_4H_{10}O \cdot 0.35\ H_2O$ (F.W.=500.008):		
	C, 73.50;	H, 6.49;	N, 5.60.
Found:	C, 73.48;	H, 6.31;	N, 5.55.

EXAMPLE 18

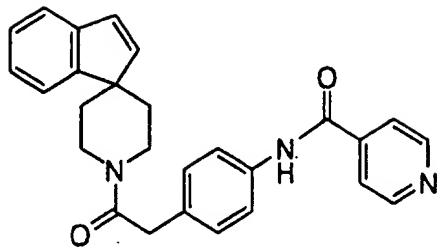


60 mg (0.188 mmol) of the product of Example 1 was dissolved in 2 ml CH2CL2 and the solution treated with 36.9 mg (0.207 mmol) of nicotinoylchloride hydrochloride. The pH of the mixture was adjusted to 9.5 with 58 µl (0.416 mmol) of triethyl amine and the reaction stirred at 25°C for 18 hours.

Flash chromatography of the reaction mixture directly on silica gel (4% MeOH in CH_2Cl_2) gave the title compound as a white solid (56.8 mg, 71.3% yield) crystallized from ether.

M.W.:	423.494.
m.p.:	205-6°C.
HPLC:	99.7%.
PMR:	Consistent with structure.
M.S.:	M+H=424 (FAB).
TLC:	R_f = 0.26, silica GF (5% MeOH in CH_2Cl_2).
CHN:	Calc'd as $C_{27}H_{25}N_3O_2$:
	C, 76.57; H, 5.92; N, 9.92.
Found:	C, 76.50; H, 5.90; N, 9.91.

EXAMPLE 19



60 ml (0.188 mmol) of the product of Example 1 was dissolved in 2 ml CH_2Cl_2 and the solution treated with 36.9 mg (0.207 mmol) of isonicotinoyl chloride hydrocloride. The pH of the mixture was adjusted to 9.5 with 58 µl (0.416 mmol) of triethylamine and the reaction stirred at 25°C for 1 hour.

Flash chromatography of the reaction mixture directly on silica gel (5% MeOH in CH_2CL_2) gave the title compound as a white solid (56.0 mg, 70.4% yield) crystallized from ether.

M.W.:	423.494.		
m.p.:	224-6°C.		
HPLC:	99.7%		
PMR:	Consistent with structure.		
M.S.:	M+H=424 (FAB).		
TLC:	R_f = 0.23, silica GF (5% MeOH in CH_2Cl_2).		
	C, 76.57;	H, 5.92;	N, 9.92.
Found:	C, 76.22;	H, 5.95;	N, 9.74.

TABLES

In addition to those compounds specifically exemplified above, additional compounds of the present invention are set forth in tabular form below. These compounds are synthesized by use of the synthetic routes and methods described in the above Schemes and Examples and variations thereof well known to those of ordinary skill in the art, and not requiring undue experimentation. All variables listed in Table 1 below are with reference to the following generic structure:

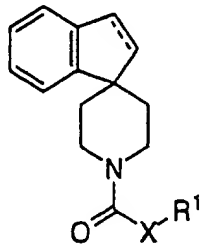


TABLE 1

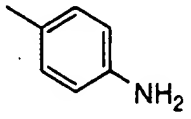
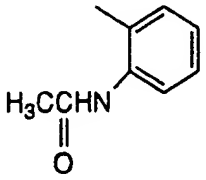
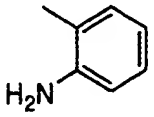
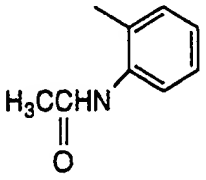
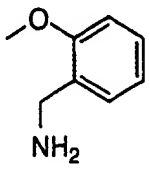
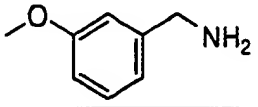
	X	R^1
5	$-CH_2-$	
10	$-CH_2-$	
15	$-CH_2-$	
20	no substituent	
25	$-CH_2-$	
30	$-CH_2-$	

TABLE 1 (CONT'D)

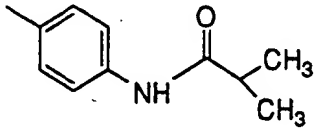
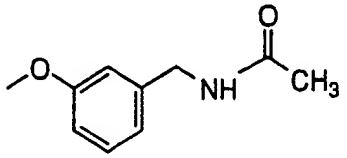
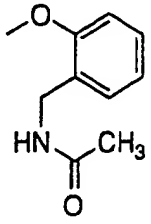
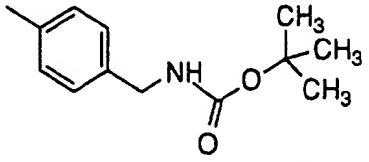
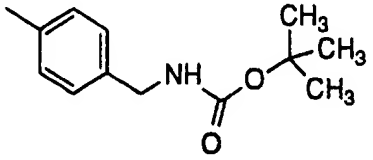
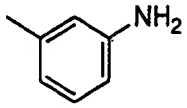
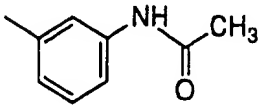
X	R^1
$-CH_2-$	H
$-CH_2-$	
$-CH_2-$	
$-CH_2-$	
$-CH_2-$	
no substituent	
$-CH_2-$	
$-CH_2-$	

TABLE 1 (CONT'D)

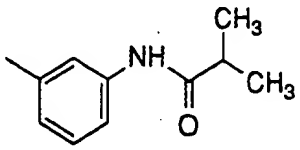
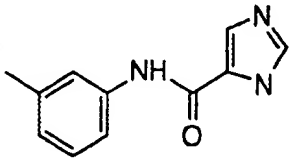
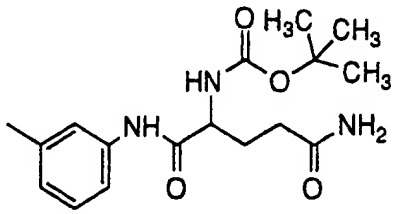
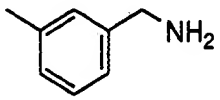
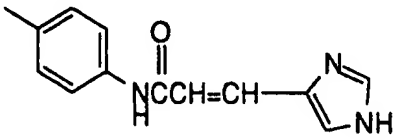
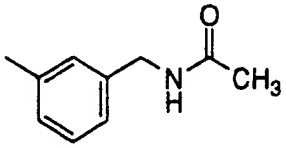
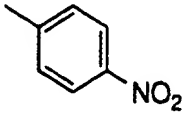
X	R^1
$-CH_2-$	
$-CH_2-$	
$-CH_2-$	
no substituent	
$-CH_2-$	
no substituent	
$-\underset{CH_3}{\overset{|}{C}}H-$	

TABLE 1 (CONT'D)

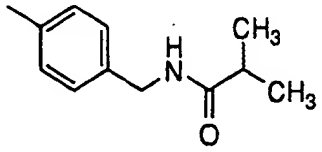
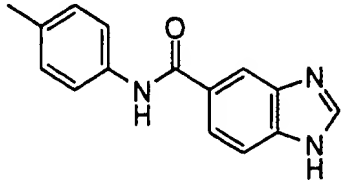
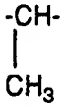
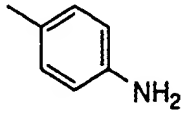
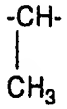
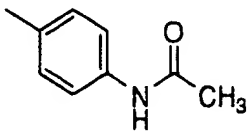
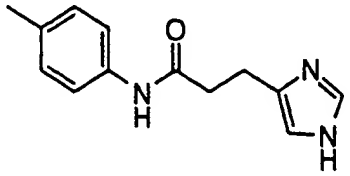
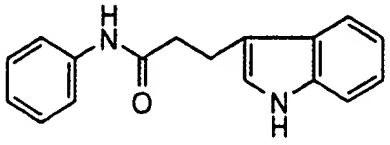
X	R^1
no substituent	
$-CH_2-$	
	
	
$-CH_2-$	
$-CH_2-$	

TABLE 1 (CONT'D)

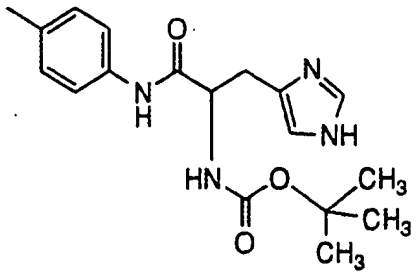
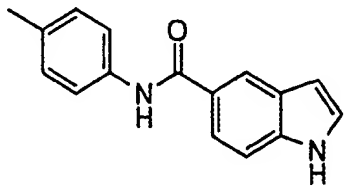
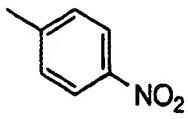
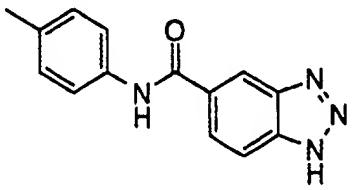
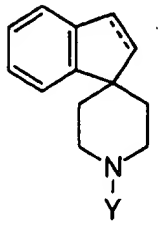
X	R^1
$-CH_2-$	
$-CH_2-$	
$-CH=CH-$	
$-CH_2-$	

TABLE 2

The variables shown in Table 2 are with reference to the following structure:



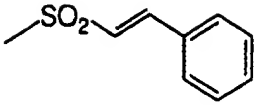
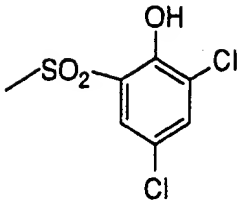
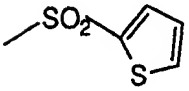
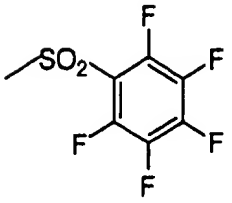
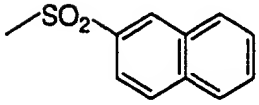
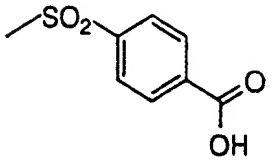
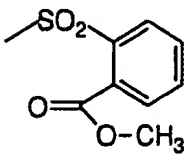
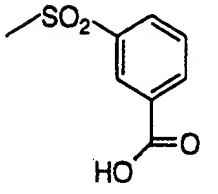
Y	Y
	
	
	
	

TABLE 2 (CONT'D)

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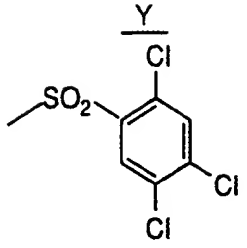	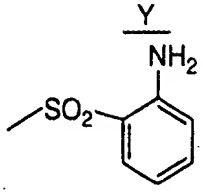
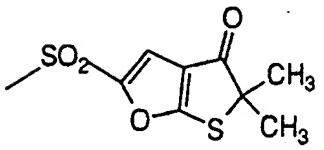	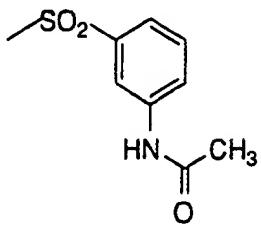
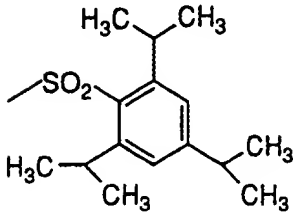	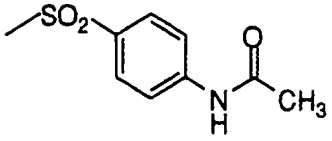
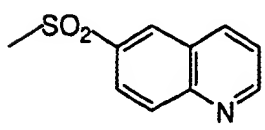	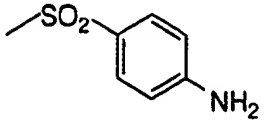
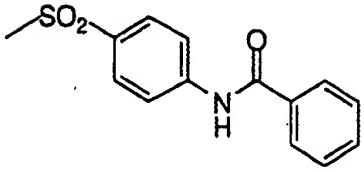	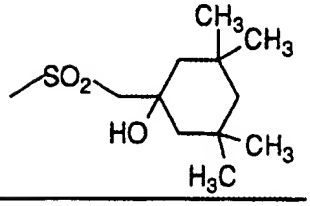

TABLE 2 (CONT'D)

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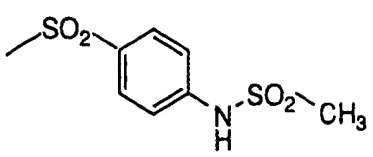	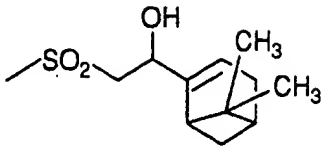
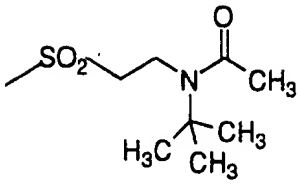	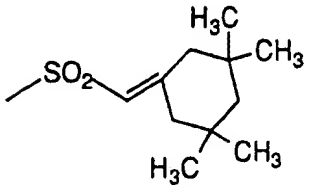
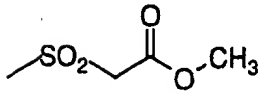	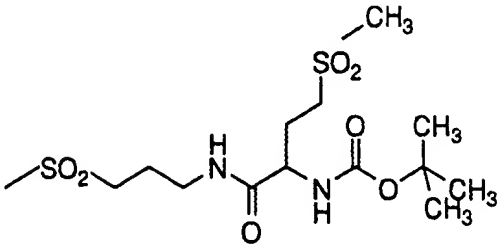
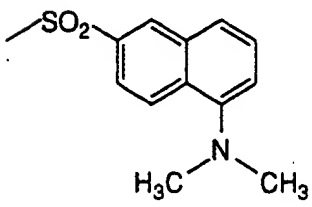	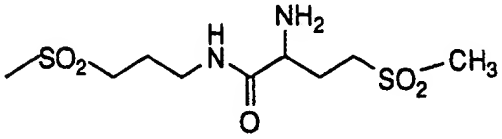
	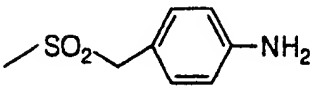

TABLE 2 (CONT'D)

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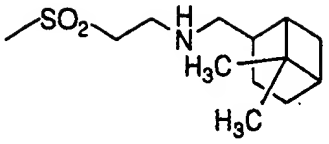
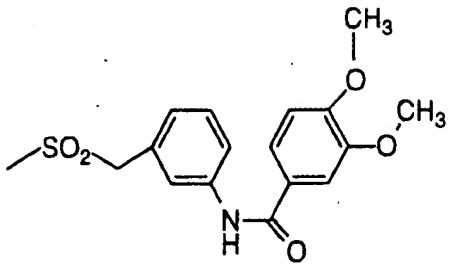
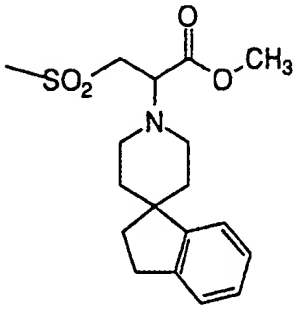
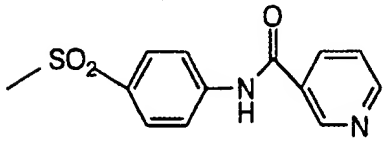
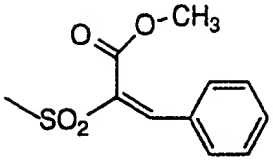
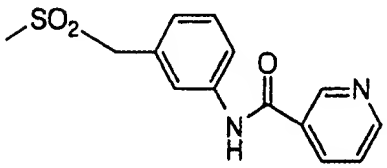
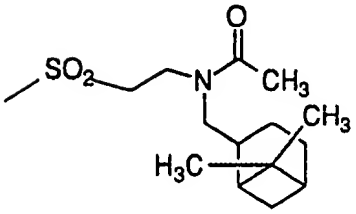
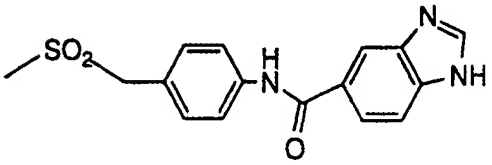
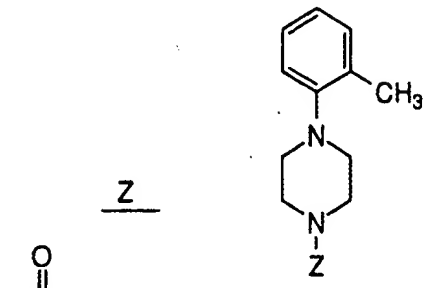
	
	
	
	

TABLE 3

The variables shown in Table 3 are with reference to the following structure:



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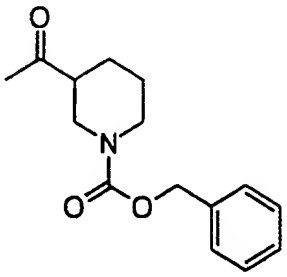	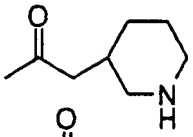
	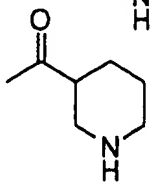
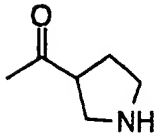	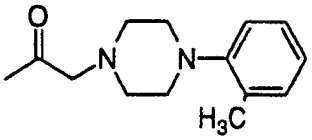
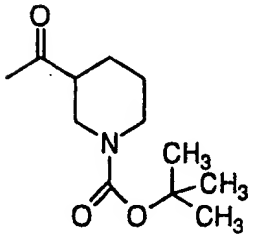	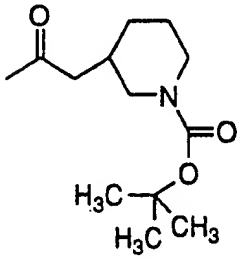
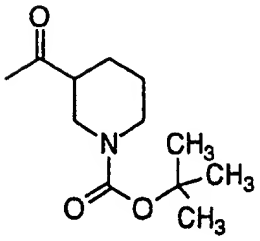	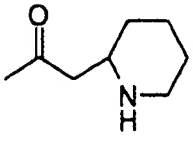

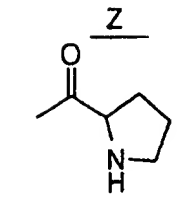
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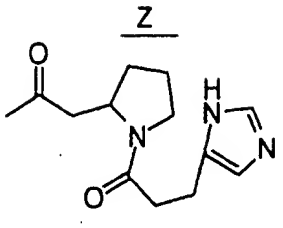
O
N
H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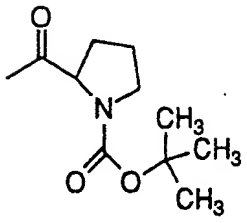
O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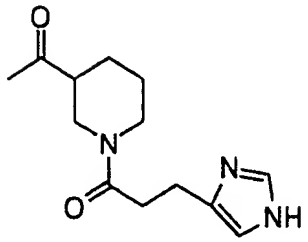
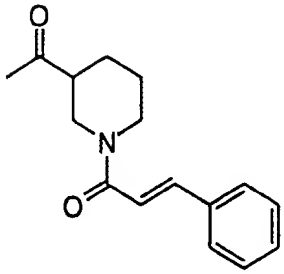
N
CH3
CH3
O
O
CH3


O
N
O
N
NH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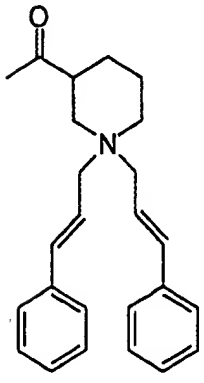
N
O


O
N

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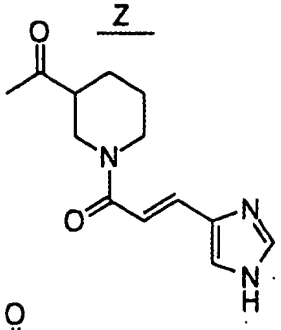

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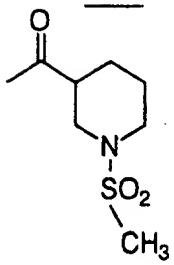

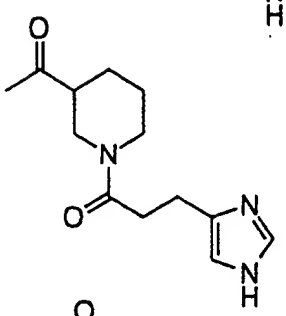

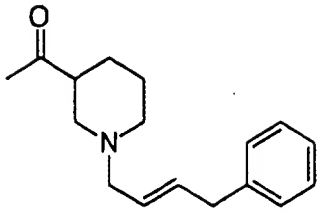

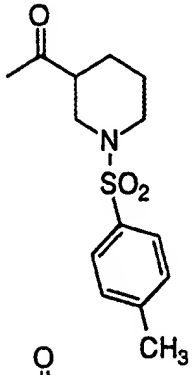

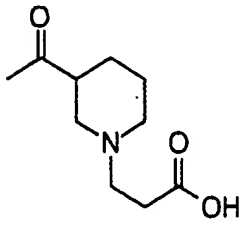

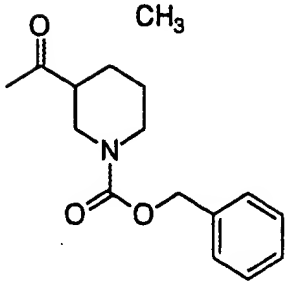

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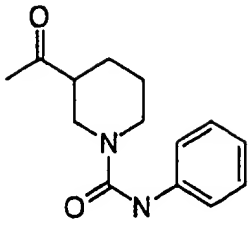	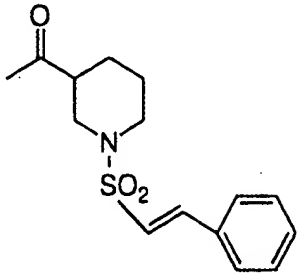
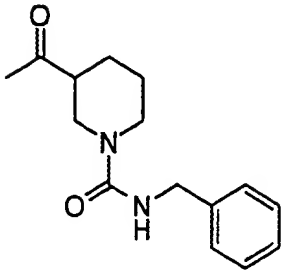	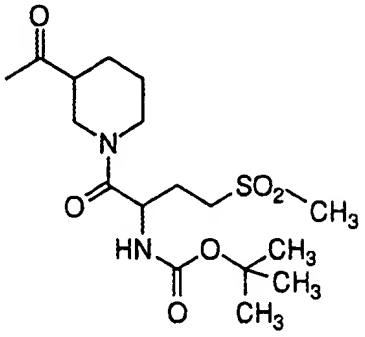
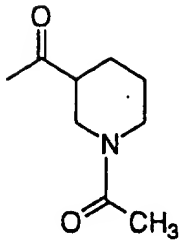	
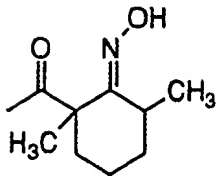	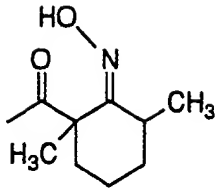

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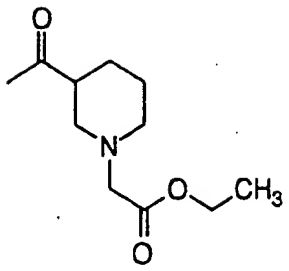
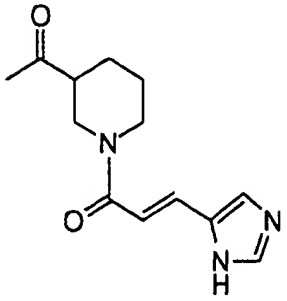
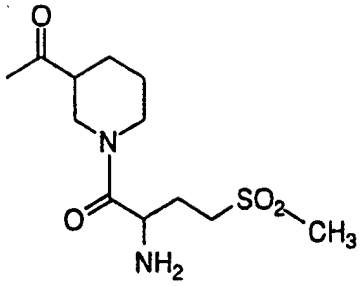
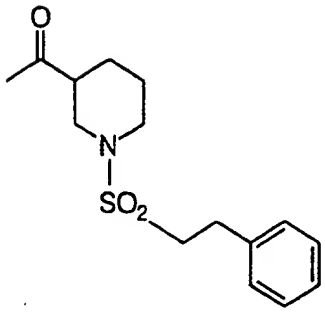








EXAMPLE 20

RADIOLIGAND BINDING ASSAYS

The high affinity binding of [^{3}H] Oxytocin (OT)([tyrosyl, 3,5-[^{3}H]OT; 30-60 Ci/mmol; New England Nuclear. Boston, MA) to uterine OT receptors was based on an assay (Fuchs, A-R; Fuchs, F; Soloff, MS. 1985 J. Clin. Endocrinol. Metab. 60:37) using a crude membrane preparation of uteri taken from diethylstilbestrol dipropionate (DES)-treated (0.3 mg/kg, ip; 18-24) rats. Competition studies were conducted at equilibrium (60 minutes; 22°C) using 1 nM[^{3}H]OT in the following assay buffer: 50 mM Tris-HCl, 5 mM $MgCl_2$, and 0.1% BSA, pH 7.4. Nonspecific binding (10% of the total binding) was determined using 1 μM unlabeled OT and the binding reaction was terminated by filtration through glass fiber filters using a cell harvester (model 7019, Skatron, Inc., Sterling, VA). IC_{50} (the concentration of tested compound that inhibits 50% of OT) was reported, unless otherwise noted.

The measurement of [^{3}H]Vasopressin (AVP) ([phenylalanyl-3,4,5-^{3}H]AVP; 80-90 Ci/mmol; New England Nuclear)binding to a crude membrane preparation of male rat liver (AVP-V_1 sites) or kidney medulla (AVP-V_2 sites) was determined according to the method of Butlen, et al. (Butlen, D; Guillon, G; Rajerison, R.M.;Jard, S; Sawyer, W.H.;Manning, M. 1978 Mol Pharmacol 14:1006).

Competition assays were conducted at equilibrium (30 minutes at 30°C) using 1 nM [^{3}H]AVP (liver) or 2 nM [^{3}H]AVP (kidney) in the following assay buffer: 100 mM Tris-HCl, 5 mM $MgCl_2$, 0.1% BSA, 50 mM phenylmethylsulfonylfluoride, and 50 mg/ml bacitracin, pH 8.0. Nonspecific binding (5-10% of the total binding) was determined using 10 μM unlabeled AVP, and the binding reaction was terminated by filtration as described above for the [^{3}H]OT binding assay.

IC_{50} values were determined for both [^{3}H]OT and [^{3}H]AVP binding assays by linear regression of the relation log concentration of compound vs. percent inhibition of specific binding.

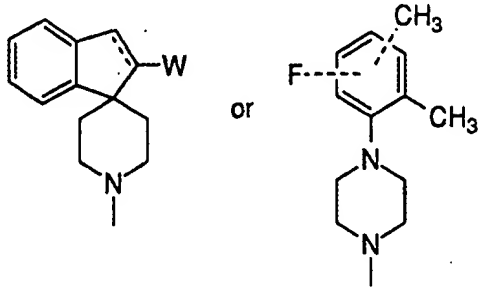
Example	IC_{50}[^{3}H]OT (nM)
10	3, 700
12	150
14	170
15	310
16	520

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for prevention of preterm labor, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound or the pharmaceutically acceptable salts and esters thereof, of the formula X-Y-Z-R^1, wherein

X is



;

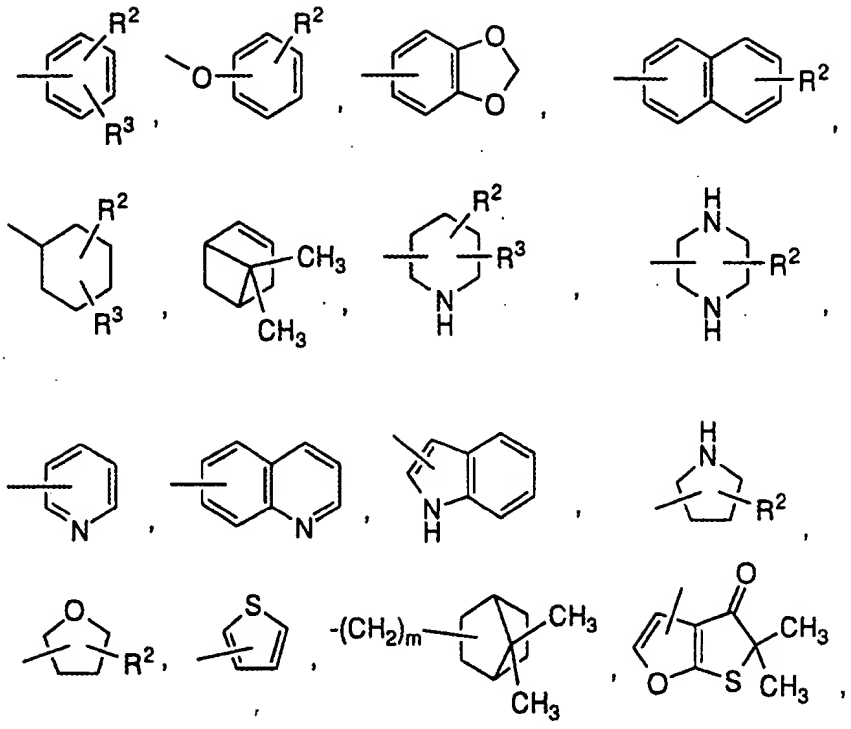
W is hydrogen or acetate;

Y is -CO-, -SO_2- -$CO(CH_2)_m$- or -$(CH_2)_m$-;

Z is an optional substituent that, when present, is one or more of N, O, S, -CHR-, -CR=CH-, -CH=, -$(CH_2)_m$- or -CHCHOH-;

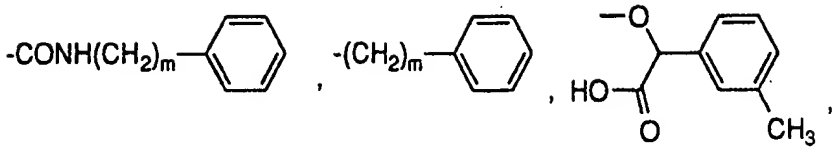
R is hydrogen, C_{1-5} alkyl or C_{1-5} alkoxycarbonylamino, quinuclidinylaminocarbonylamino;

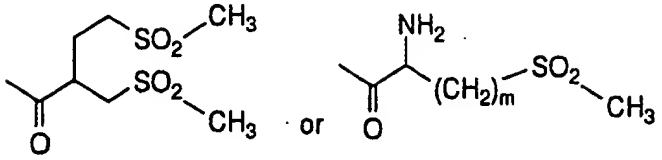
R^1 is -CH_3, -$CH(CH_3)_2$, C_{1-5} alkoxycarbonyl,



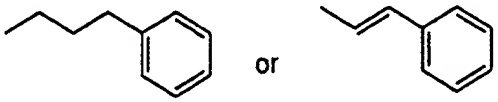
$-NR^4R^5$ or $-NCOR^6$;

R^2 is hydrogen, hydroxy, carboxyl, acetyl, cis or trans oximino, nitro, halogen,
mono-, di- or tri-C_{1-3} alkyl, spirocyclic indenyl,
N-spiroindanepiperidinyl, C_{1-5} alkoxy, O-Het where Het is imidazole or benzimidazole or azimidobenzene, or where R^2 is further defined as $-COR^6$, $-(CH_2)_m-NHCOR^7$, $-(CH_2)_mNHCOOR^7$, $-(CH_2)_m-NR^8R^9$, $-(CH_2)_m-NHCO-(CH_2)_mR^7$, $-(CH_2)_m-NHCO-CHR^7R^7$, $-(CH_2)_m-NHCO-CH=CHR^7$, $-(CH_2)_m-CO-O-R^7$, $-(CH_2)_m-CO-O-(CH_2)_mR^7$, $-(CH_2)_m-CO-O-CHR^7R^7$, $-(CH)_m-CO-O-CH=CHR^7$, $-NHSO_2R$-where R is as defined above, $NHSO_2R^7$, $-(CH_2)_m-O-R^{10}$, $-SO_2R^{10}$, $-COR^{11}$,





or one to two substituents selected from the group consisting of



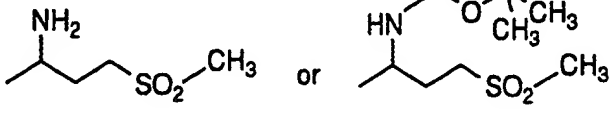
;

R^3 is one or two of hydrogen, hydroxyl or C_{1-5} alkyl;

with the proviso that when R^1 is cyclohexyl, then R^2 and R^3 are limited to hydroxyl or C_{1-5} alkyl;

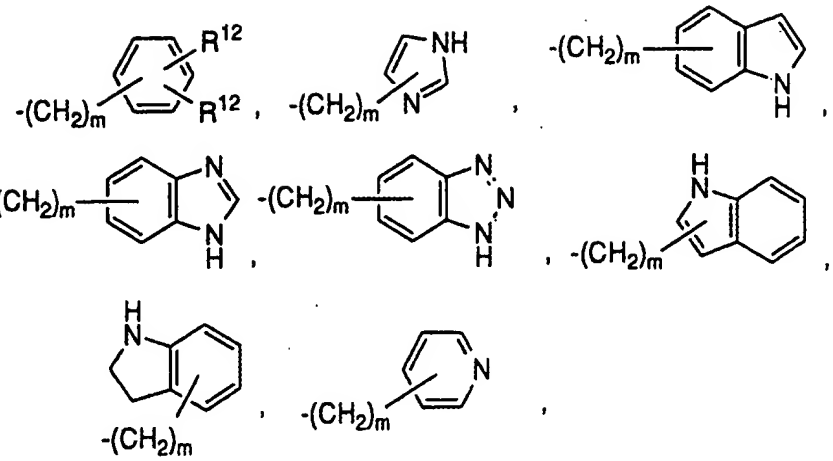
R^4 is hydrogen, C_{1-5} alkyl, or C_{6-10} cycloalkyl;

R^5 is hydrogen or acetyl;

R^6 is 

;

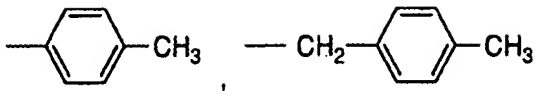
R^7 is

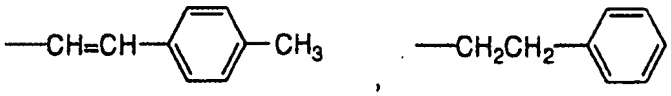


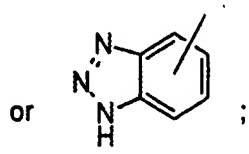
hydrogen, C_{1-4} alkyl, NSO_2R^{12} or NHO-C_{1-4} alkyl;

R^8 is hydrogen or C_{1-5} alkyl;
R^9 is hydrogen or C_{1-5} alkyl;

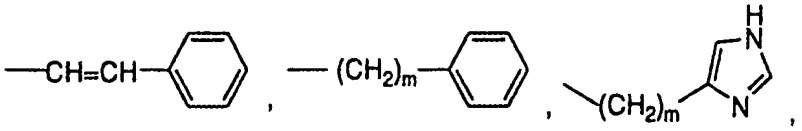
R^{10} is $-CH_3$,

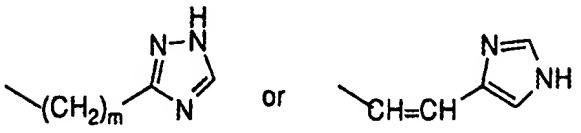






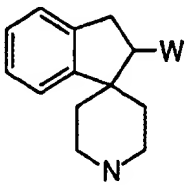
R^{11} is -CH_3,





R^{12} is hydrogen, C_{1-5} alkyl or C_{1-5} alkoxy; and

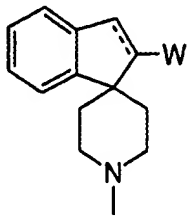
m is an integer of from 0 to 5;



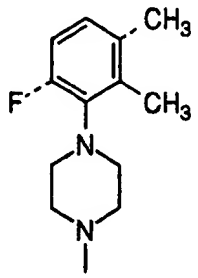
with the proviso that when X is

and when R^1 is disubstituted phenyl when the phenyl substituents are any of hydroxyl, carboxyl, nitro, halogen, mono-, di- or tri-C_{1-3} alkyl, C_{1-5} alkoxy; or when R^1 is pyridyl; or when R^1 is $-CH_3$ or $-CH(CH_3)_2$; or when R^1 is unsubstituted bicyclo loweralkyl of 9 carbons or unsubstituted or substituted cyclohexyl and the substituent is hydroxyl; then Y is $-(CH_2)_m-$ where m has a value of from 1 to 5.

2. A compound as claimed in Claim 1, wherein X is



3. A compound as claimed in Claim 1, wherein X is



4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmacologically effective amount of the compound as claimed in Claim 1 sufficient to prevent preterm labor in a mammal in need thereof.

5. A method of antagonizing oxytocin from binding to its receptor site in a mammal, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

6. A method of preventing preterm labor in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

7. A method stopping labor preparatory to cesarian delivery in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

8. A method of treating dysmenorrhea in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

9. A method of antagonizing vasopressin from binding to its receptor site in a mammal, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

10. A method of inducing vasodilation in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

11. A method of treating hypertension in a mammal in need thereof, comprising the step of administering to said mammal a

pharmacologically effective amount of the compound as claimed in Claim 1.

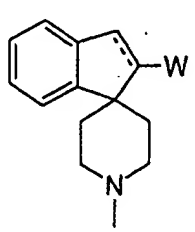
12. A method of inducing diuresis in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

13. A method of inhibiting platelet agglutination in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

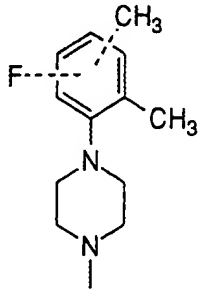
AMENDED CLAIMS
[received by the International Bureau on 4 March 1994 (04.03.94);
original claim 1 amended; other claims unchanged (4 pages)]

1. A compound or the pharmaceutically acceptable salts and esters thereof, of the formula X-Y-Z-R^1, wherein

X is



or



;

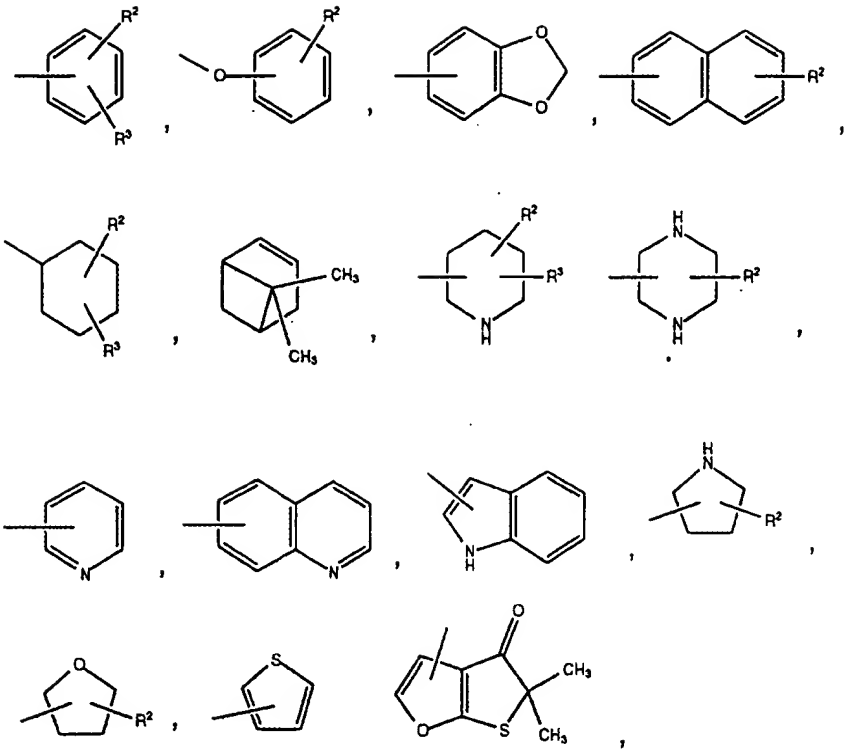
W is hydrogen or acetate;

Y is -CO- or -SO_2-;

Z is an optional substituent that, when present, is one or more of N, O, S, -CHR-, -CR=CH-, -CH=, -$(CH_2)_m$-CHR-, -$(CH_2)_m$- or -CHCHOH-;

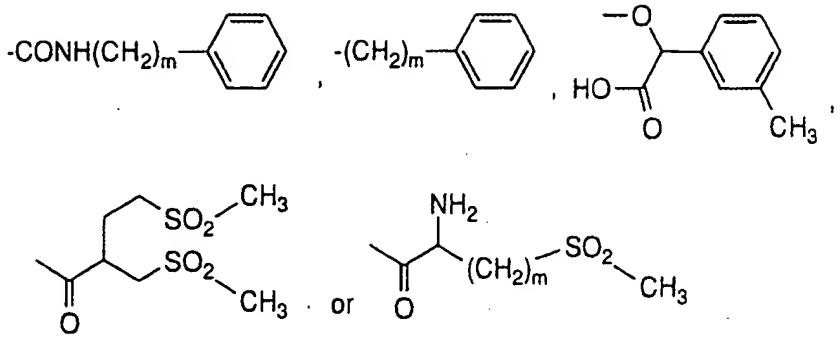
R is hydrogen, C_{1-5} alkyl or C_{1-5} alkoxycarbonylamino, quinuclidinylaminocarbonylamino;

R^1 is -CH_3, -$CH(CH_3)_2$,

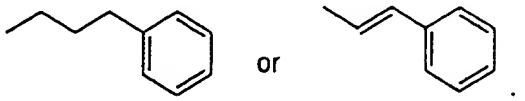


$-NR^4R^5$ or $-NCOR^6$;

R^2 is hydrogen, hydroxy, carboxyl, acetyl, cis or trans oximino, nitro, spirocyclic indenyl, N-spiroindanepiperidinyl, O-Het where Het is imidazole or benzimidazole or azimidobenzene, or where R^2 is further defined as $-COR^6$, $-(CH_2)_m-NHCOR^7$, $-(CH_2)_mNHCOOR^7$, $-(CH_2)_m-NR^8R^9$, $-(CH_2)_m-NHCO-(CH_2)_mR^7$, $-(CH_2)_m-NHCO-CHR^7R^7$, $-(CH_2)_m-NHCO-CH=CHR^7$, $-(CH_2)_m-CO-O-R^7$, $-(CH_2)_m-CO-O-(CH_2)_mR^7$, $-(CH_2)_m-CO-O-CHR^7R^7$, $-(CH)_m-CO-O-CH=CHR^7$, $-NHSO_2R$-where R is as defined above, $NHSO_2R^7$, $-(CH_2)_m-O-R^{10}$, $-SO_2R^{10}$, $-COR^{11}$,



or one to two substituents selected from the group consisting of



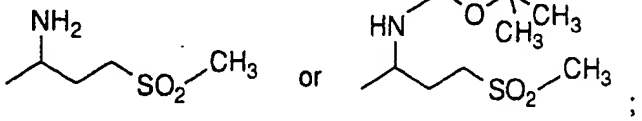
;

R^3 is one or two of hydrogen or hydroxyl;

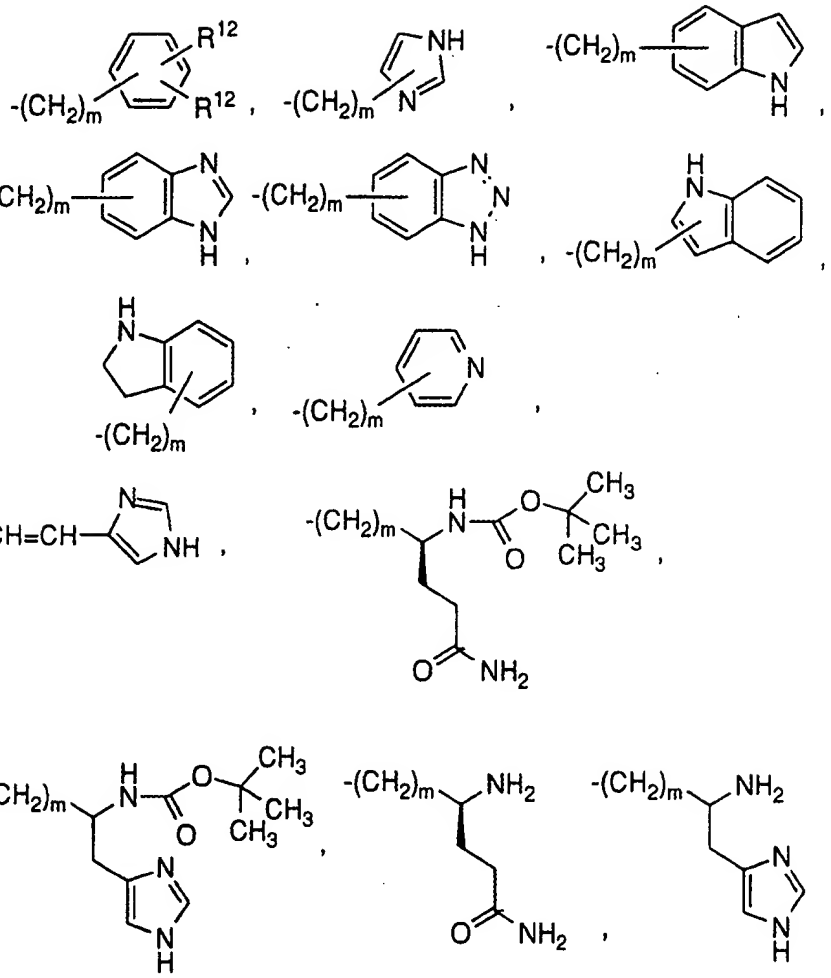
with the proviso that when R^1 is cyclohexyl, then R^2 and R^3 are limited to hydroxyl or C_{1-5} alkyl;

R^4 is hydrogen, C_{1-5} alkyl, or C_{6-10} cycloalkyl;

R^5 is hydrogen or acetyl;

R^6 is  ;

R^7 is



hydrogen, NSO_2R^{12} or NHO-C_{1-4} alkyl;

R^8 is hydrogen or C_{1-5} alkyl;
R^9 is hydrogen or C_{1-5} alkyl;

R^{10} is $-CH_3$,

INTERNATIONAL SEARCH REPORT

Inte...ational application No.
PCT/US93/09152

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :Please See Extra Sheet.
US CL :514/278; 546/17; 544/230
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/278; 546/17; 544/230

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS on line for structure.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A, 0,445,974 (Billington et al) 09 November 1991. See Page 7, lines 2, 4, 11, 12, 13; Ex. 1, Step 2; Page 6, last 4 lines.	1,2,4
X	US,A, 5,091,387 (Evans) 25 February 1992. See Claim 1 and Ex. 2-7, 23, 24, 30.	1,2,4-8
A	EP,A, 0,414,289 (Billington et al) 27 February 1991. See entire document.	1,2,4-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 21 DECEMBER 1993	Date of mailing of the international search report 10 JAN 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer MARK BERCH ACH Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/09152

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(Telephone Practice)
Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1,2,4-8

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int...ational application No.
PCT/US93/09152

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):

A61K 31/445, 31/495, 31/47; C07D 221/20, 401/06, 401/12, 401/14, 403/06, 403/12, 403/14, 409/06, 409/12, 409/14, 493/04.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I. Claim 1 (part), 2, 4-8 (part), drawn to spiropiperidines, classified in Class 546, subclass 17.

II. Claim 1 (part), 3, 4-8 (part), drawn to piperizines, classified in Class 544, subclasses 360, 363, 362, 364, 365, 366, 370, 372, 373, 374, 376, 377, 379, 383, 389, 390-395.

III. Claims 6-13 (part), drawn to other uses for Gp. I compounds, classified in Class 514, subclass 278.

IV. Claims 6-13 (part), drawn to other uses for Group II compounds, classified in Class 514, subclass 255.

Group I and II are distinct as seen by their markedly different chemical structure. Group I is a spiro ring assembly, Group II is not. Group II has a ring with 2 hetero-atoms; Group I does not. Group II requires a Fluorine and 2 methyls; Group I does not even permit these.

By "other uses" is meant other than those of claims 5-8.

With regard to Group III and IV, these utilities appear to be separate and unrelated to the pharmaceutical activity in claim 5 and hence are a distinct utility.